



**sanofi aventis**

Because health matters

rec'd MB  
6.7.07

May 16, 2007

**BY HAND DELIVERY**

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

**CITIZEN PETITION**

Sanofi-aventis U.S. LLC, a subsidiary of sanofi-aventis, and successor in interest to Sanofi-Synthelabo ("sanofi-aventis"), submits this Citizen Petition under section 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") (21 U.S.C. §§ 355(b) and (j)) and 21 C.F.R. § 10.30, to request that the Commissioner of Food and Drugs take special consideration when reviewing any abbreviated new drug application ("ANDA") for a generic version of AMBIEN CR™ (zolpidem tartrate extended-release tablets) ("AMBIEN CR"). Sanofi-aventis is the manufacturer and distributor of AMBIEN CR, a non-benzodiazepine hypnotic of the imidazopyridine class.

**I. Actions Requested**

Sanofi-aventis requests that the agency take special consideration when reviewing any application for a generic version of AMBIEN CR. Due to the formulation of the AMBIEN CR product, the entire plasma profile defines the safety and effectiveness of AMBIEN CR beginning with the onset of activity through post-awakening. Deviations from this plasma profile have the potential to affect one or more key characteristics of the clinical hypnotic profile of the product, and the traditional FDA bioequivalence parameters ( $C_{max}$  and AUC) are unlikely to predict the pharmacodynamic impact of differences in plasma drug concentrations. While FDA's standard of bioequivalence, requiring  $C_{max}$  and AUC to show 90% confidence intervals within 80-125% of the reference drug, is generally adequate to assure bioequivalence, in the case of extended-release sedative hypnotics, which not only require early sleep induction and sleep maintenance, but alertness upon awakening, these parameters alone may not be adequate. FDA should rely upon more specific pharmacokinetic parameters to assure generics to AMBIEN CR will be

2007P.0224

CPI

May 16, 2007

Page 2

clinically equivalent. Sanofi-aventis suggests that generics demonstrate equivalence as a function of time such as  $AUC_{0-3hr}$ ,  $AUC_{3-6hr}$  and  $AUC_{6-\infty}$  in addition to the traditional FDA bioequivalence parameters ( $C_{max}$  and AUC), as appropriate surrogates to assure clinical equivalence to AMBIEN CR. Sanofi-aventis also requests that FDA require generics to AMBIEN CR to include immediate release and extended-release properties in their formulation in order to assure the generic will have similar sleep induction and sleep maintenance capabilities as well a similar safety profile over the full night of sleep (7-8 hours), particularly upon awakening.

## II. Brief Statement of Grounds

Pursuant to section 505(j)(2)(A)(iv) of the FDCA, any ANDA must contain, among other things, information demonstrating that the generic drug is bioequivalent to the reference listed drug ("RLD").<sup>1</sup> In most instances, FDA will statistically evaluate two pharmacokinetic parameters -- area under the plasma concentration curve (AUC) and the peak drug concentration ( $C_{max}$ ) -- to determine bioequivalence.<sup>2</sup> According to the FDA, to establish bioequivalence, the calculated 90% confidence interval for the ratios comparing the average AUC and  $C_{max}$  values between the generic applicant and the RLD should fall within the traditional bioequivalence limit of 80% to 125%.<sup>3</sup> In response to citizen petitions requesting that the agency impose additional bioequivalence requirements, FDA has consistently defended its traditional bioequivalence parameters, studies, and testing procedures. Although the agency has acknowledged the importance of evaluating other pharmacokinetic parameters, such as  $C_{min}$ , Ct,  $T_{max}$ , and  $T_{lag}$ , to determine bioequivalence with respect to certain classes of drugs, FDA has not strayed so far from its traditional evaluation methods as to require rigid statistical analysis for such parameters.

Due to the nature of AMBIEN CR's formulation, its sleep induction and maintenance indications, and the specific safety concerns associated with hypnotic therapy, the current FDA requirements that only  $C_{max}$  and AUC need to be presented as a demonstration of bioequivalence are insufficient to ensure that generic versions of AMBIEN CR are therapeutically equivalent to AMBIEN CR. Based on the FDA requirements for bioequivalence, it is highly conceivable that a generic formulation of AMBIEN CR with a different pharmacokinetic profile ("shape of the curve") could be approved as a bioequivalent and substitutable generic product.

---

<sup>1</sup> See 21 U.S.C. § 355(j)(2)(A)(iv).

<sup>2</sup> See FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (March 2003) ("March 2003 Guidance").

<sup>3</sup> See FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (January 2001), page 2; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Chapter 1.3, "Statistical Criteria for Bioequivalence" (2003).

May 16, 2007

Page 3

The AMBIEN CR formulation differs in important ways from most extended release products. Generally, extended release preparations are developed with the primary goal of reducing the number of daily doses needed to sustain an effect of a chronically administered drug product that is rapidly cleared from the system. This fosters improved compliance and reduces the incidence of adverse effects associated with peak plasma concentrations and periods of inactivity associated with valleys in the plasma levels (reduction in peak to trough fluctuations). The major difference between the extended release zolpidem formulation, AMBIEN CR, and typical extended release formulations is the combined need with AMBIEN CR for an appropriately rapid onset of activity, maintenance of activity for a prolonged period, and reliable cessation of drug activity. Reliable cessation of activity is not a common concern for most extended release preparations. Residual effectiveness of a drug product as plasma levels decline does not normally have the potential to interfere with the ability of a patient to function. For a sleep medication, however, residual effects experienced in the morning after use have the potential to negate any benefits accrued from achieving a full night of sleep. Thus, the entire plasma profile defines the safety and effectiveness of AMBIEN CR from onset to cessation of activity. Deviations from this profile have the potential to affect one or more key characteristics of the clinical hypnotic profile of the product. These differences can lead to significant consequences for patients. If extended-release zolpidem formulations have different pharmacodynamic profiles, it would present a rather peculiar problem for physicians and patients, because one would not know how the drug was going to perform, if at all effectively.

The differences in pharmacodynamic profiles may not be apparent based just on a comparison of  $C_{max}$  and AUC, and thus, generic formulations should be required to demonstrate a greater concurrence of plasma concentration-time curves than are reflected in just bioequivalent  $C_{max}$  and AUC values. Because the total plasma concentration-time profile of AMBIEN CR can be associated with three important qualities of sedative hypnotics -- time to sleep onset, maintenance of sleep, and lack of residual effects -- Sanofi-aventis requests that FDA take special consideration when reviewing any application for a generic version of AMBIEN CR. Sanofi-aventis requests that the agency utilize specific bioequivalence requirements that better assure clinical equivalence between generic zolpidem extended release drug products and AMBIEN CR and require generic applicants seeking approval of a therapeutically equivalent generic of AMBIEN CR to include immediate and extended-release components in their tablets.

### **III. Complete Statement of Grounds**

#### **A. AMBIEN CR**

AMBIEN CR contains either 6.25 mg or 12.5 mg zolpidem tartrate, in a specific ratio of immediate and extended-release formulation for oral administration. AMBIEN CR consists of a coated two-layer tablet: one layer releases its drug content immediately and another layer allows for a slower release of zolpidem tartrate. AMBIEN CR is an extended release preparation developed to meet the unique needs of individuals suffering from more than one symptom of

May 16, 2007

Page 4

insomnia: (1) difficulty in falling asleep, and (2) difficulty in maintaining sleep through the night. Importantly, the product was also developed with the goal of allowing individuals to awaken in the morning without experiencing residual adverse drug effects on cognitive or psychomotor functioning. The immediate release formulation of zolpidem (Ambien<sup>®</sup>) is rapidly and nearly completely absorbed from the gastrointestinal tract with a limited first-pass effect. This allows plasma levels to rise quickly and induce sleep. The immediate-release formulation is also metabolized to inactive metabolites. The plasma elimination half-life of approximately 2.5 hours allows drug to clear sufficiently quickly to avoid residual effects after a typical 7-8-hour period of sleep. However, the short half-life interferes with the ability of the drug to maintain sleep in the middle of the night.<sup>4</sup> Increasing the amount of zolpidem in the immediate-release formulation was not a viable option for assuring sufficiently elevated plasma levels during the middle of the night because of an increased risk of adverse effects. In the clinical trials with immediate-release Ambien<sup>®</sup>, there was subjective evidence of certain central nervous system adverse events occurring predominantly at doses above 10 mg.<sup>5</sup> To meet the goals of rapid sleep onset, maintenance of sleep during the middle of the night, and wakefulness without residual effects after 7-8 hours of sleep, it was determined that an alternative formulation be developed.

The parameters for the release of zolpidem from the AMBIEN CR extended release formulation that is currently marketed were carefully selected from eight potential formulations to maximize efficacy and safety according to these parameters. In the Agency's Clinical Pharmacology and Biopharmaceutics Review of the AMBIEN CR new drug application ("NDA"), FDA reviewers concluded that the currently marketed version of AMBIEN CR "appeared to be the optimal selection, with increase[d] duration of activity (especially in the middle of the night) and lack of residual effects 8 and 9 hours postdosing."<sup>6</sup> The FDA reviewers further noted that formulations that varied from the Phase III formulation "did not fulfill expected criteria in terms of increase in duration of activity without residual effect."<sup>7</sup>

---

<sup>4</sup> E. Weinling, et. al, "Pharmacokinetic Profile of a New Modified Release Formulation of Zolpidem Designed to Improve Sleep Maintenance. *Fundamentals of Clinical Pharmacology*. 2006 Aug; 20(4):397-403.

<sup>5</sup> See Ambien (zolpidem tartrate) Prescribing Information, March 2007.

<sup>6</sup> See Clinical Pharmacology and Biopharmaceutics Review(s), Application Number: 21-774, Center for Drug Evaluation and Research, at 9; available at: [http://www.fda.gov/cder/foi/nda/2005/021774s000\\_BioPharmR.pdf](http://www.fda.gov/cder/foi/nda/2005/021774s000_BioPharmR.pdf).

<sup>7</sup> See *id.* at 8.

May 16, 2007

Page 5

## **B. Statutory and Regulatory Background: Bioequivalence**

Pursuant to section 505(j)(2)(A)(iv) of the FDCA, any ANDA must contain, among other things, information demonstrating that the generic drug is bioequivalent to the reference listed drug.<sup>8</sup> The Act further states that, for purposes of an ANDA, bioequivalence is established if:

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.<sup>9</sup>

The statute defines “bioavailability” as “the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from the drug and becomes available at the site of drug action.”<sup>10</sup> As a result, generic drugs often attempt to establish bioequivalence through what is essentially a showing of equivalent bioavailability to the RLD. FDA’s regulations appear to sanction this approach stating:

Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.<sup>11</sup>

## **C. FDA’s March 2003 Guidance**

In the March 2003 Guidance, FDA recommends two studies to demonstrate bioequivalence for generic versions of modified-release products (which FDA has defined to include both delayed-release and extended-release products). The first study being a single-dose, nonreplicate, fasting study comparing the highest strength of the test and reference listed drug product and the second study being a food-effect, nonreplicate study comparing the highest

---

<sup>8</sup> See 21 U.S.C. § 355(j)(2)(A)(iv).

<sup>9</sup> 21 U.S.C. § 355(j)(8)(B)(i).

<sup>10</sup> 21 U.S.C. § 355(j)(8)(A).

<sup>11</sup> 21 C.F.R. § 320.23(b).

May 16, 2007

Page 6

strength of the test and reference product.<sup>12</sup> FDA states that for orally administered immediate-release drug products, bioequivalence can generally be demonstrated by two pharmacokinetic parameters -- area under the plasma concentration curve (AUC) and the peak drug concentration ( $C_{max}$ ).<sup>13</sup> FDA generally requires these same parameters for modified-release products. According to the agency, to establish bioequivalence, the calculated 90% confidence interval for the ratios comparing the average AUC and  $C_{max}$  values between the generic applicant and the RLD should fall within the traditional bioequivalence limit of 80% to 125%.<sup>14</sup>

FDA discusses the use of an early exposure metric that may be used as a more sensitive measure of absorption rate between two products ("partial AUC") in the March 2003 Guidance,<sup>15</sup> but the agency does not appear to have required the use of this metric as an additional criteria to demonstrate bioequivalence between a generic test product and the reference product. As mentioned above, in response to citizen petitions requesting that the agency impose additional bioequivalence requirements, FDA has consistently defended its traditional bioequivalence parameters, studies, and testing procedures. Even for narrow therapeutic range drugs, FDA has explicitly stated, "[u]nless otherwise indicated by a specific guidance, [FDA] recommends that the traditional BE limit of 80 to 125 percent for non-narrow therapeutic range drugs remains unchanged for the bioavailability measures (AUC and  $C_{max}$ ) of narrow therapeutic range drugs."<sup>16</sup>

**D. FDA's Traditional Bioequivalence Parameters Are Not Adequate to be Used to Establish Bioequivalence Among Extended-Release Zolpidem Formulations**

Sanofi-aventis has received written communication from six companies stating they had developed and filed ANDAs for generic zolpidem tartrate extended release. Furthermore, the ANDA applicants included certifications in their applications that their specific formulations did not infringe the patent covering AMBIEN CR or that they considered the patent to be invalid. In order to be considered ANDAs acceptable for FDA review, sanofi-aventis believes FDA conducted an initial evaluation to confirm bioequivalence was demonstrated to AMBIEN CR by the traditional parameters -  $C_{max}$  and AUC within the accepted bioequivalence limits (0.80 -

---

<sup>12</sup> March 2003 Guidance at 16.

<sup>13</sup> *Id.* at 8.

<sup>14</sup> See FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (January 2001), page 2; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Chapter 1.3, "Statistical Criteria for Bioequivalence" (2006).

<sup>15</sup> March 2003 Guidance at 8-9.

<sup>16</sup> *Id.* at 20.

May 16, 2007

Page 7

1.25). Because sanofi-aventis has a patent for the unique in vitro release of AMBIEN CR, some of the generic applicants, as stated in their respective detailed statement of factual and legal basis of noninfringement, purposely formulated their drug products with in vitro release properties "significantly" or "markedly" different from that of AMBIEN CR so as not to infringe AMBIEN CR's patent (which, among other things, requires that 40%-70% of drug be released in the first 30 minutes, and the time for release of 90% of the total amount of zolpidem is between 2 and 6 hours).

Sanofi-aventis recognizes different formulations could produce different in vitro dissolution profiles while producing similar in vivo release rates. However, sanofi-aventis is concerned by the formulation descriptions provided by some of the generic applicants.<sup>17</sup> Three applicants claim their drug products do not include a rapid release phase, but only a monophasic extended release, with an in vitro release less than 40% of the active ingredient within the first 30 minutes. Sanofi-aventis is skeptical that these monophasic products, without an immediate release component, will have similar sleep induction properties to AMBIEN CR. In addition, their monophasic "significantly" slower dissolution rate might produce a higher concentration of zolpidem after 8 hours post dose than AMBIEN CR. As described later in the petition, this may cause an increased incidence of residual psychomotor and cognitive side effects. On the other hand, another generic applicant claims its extended-release formulation releases "markedly" more than 70% of active ingredient within 30 minutes. Without knowing the specific in vitro and in vivo dissolution profile of this product, there is a potential this product is primarily an immediate release formulation and will produce middle of the night blood concentrations lower than AMBIEN CR. As described later in the petition this will potentially reduce the product's ability to maintain sleep during the middle of the night equivalent to AMBIEN CR.

As stated in the FDA approved labeling, "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."<sup>18</sup> These properties are essential to the pharmacodynamic and clinical characteristics of the product.

Based on the biopharmaceutic properties of zolpidem and AMBIEN CR's in vitro release properties, sanofi-aventis developed a Level A (the highest level) in-vivo in-vitro correlation (IVIVC) for AMBIEN CR as part of the regulatory development program, which was found

---

<sup>17</sup> These descriptions were provided through nonconfidential disclosures from the generic applicants.

<sup>18</sup> See AMBIEN CR Prescribing Information, April 2007.

May 16, 2007

Page 8

acceptable by the Agency.<sup>19</sup> The IVIVC was used to generate predicted plasma profiles for formulations with different dissolution properties (see Appendix A). Sanofi-aventis has concluded that the pharmacodynamic and clinical characteristics of generic products with pharmacokinetic curves with different shapes than AMBIEN CR may have important clinical differences. These include differences in the ability to induce sleep, the ability to maintain sleep during the middle of the night, and/or the ability to awaken without residual effects on cognitive or psychomotor functioning.

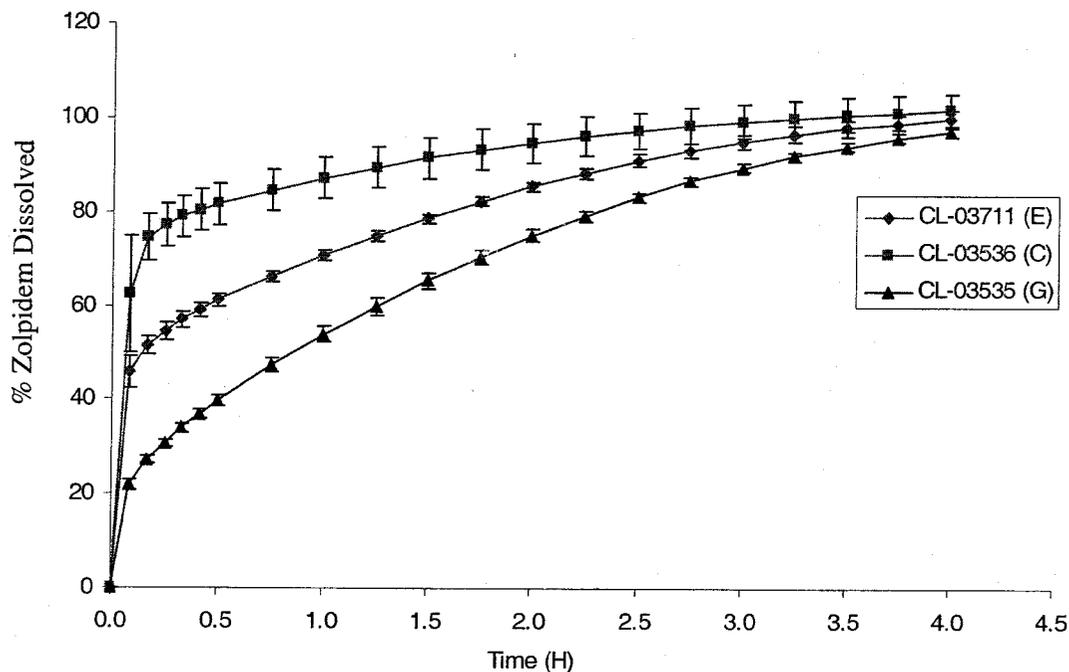
**Formulations with identical dosages but different release rates produced differences in efficacy and safety**

During the development of AMBIEN CR, several different formulations varying in dose and release properties were tested for clinical efficacy and safety. This included three different 12.5 mg zolpidem formulations, each with a different ratio of IR and ER fractions. Analysis of the in vitro release rates of these three extended release formulations containing 12.5 mg of zolpidem tartrate showed that release of the active ingredient was essentially complete for each formulation by 4 hours, but that rates of release during that period were quite different (Figure 1). One of these 12.5 mg formulations (CL-03711, Formulation E) exhibited an initially rapid in vitro release of approximately 60% of the active ingredient within 30 minutes followed by a slower rate of release of the remaining 40% of active. Another of the 12.5 mg formulations (CL-03536, Formulation C), with a larger proportion of IR, released a larger proportion (80%) of the total drug initially followed by a very slow increment in release of the additional 20% over the remainder of the 4-hour period. The final 12.5 mg formulation (CL-03535, Formulation G), with the lowest proportion of IR, had the lowest initial in vitro release (approximately 40% released in the first 30 minutes) followed by a steep increase in rate of release of the additional 60% over the remainder of the 4-hour period. The 12.5 mg formulation with the intermediate release characteristics (Formulation E) was selected for development based on its clinical efficacy and safety profile (see below).

---

<sup>19</sup> See Clinical Pharmacology and Biopharmaceutics Review(s), Application Number: 21-774, Center for Drug Evaluation and Research, at 15; available at: [http://www.fda.gov/cder/foi/nda/2005/021774s000\\_BioPharmR.pdf](http://www.fda.gov/cder/foi/nda/2005/021774s000_BioPharmR.pdf).

**Figure 1. In Vitro Drug Release Profiles from Three Different 12.5 mg Zolpidem Formulations**



Using the results of the established IVIVC (see Appendix A) it is possible to predict the plasma concentration profile based on dissolution data for the 12.5 mg formulation with the lowest proportion of IR (slow releasing Formulation G) described above. The predicted plasma profile for Formulation G is shown in Figure 2. This may be contrasted with actual plasma concentrations obtained in the clinical pharmacokinetic trial, GAR4624<sup>20</sup> for the 12.5 mg zolpidem formulation that contained the proportion of IR and ER that was chosen for development and marketing as AMBIEN CR (intermediate releasing Formulation E). This comparison reveals substantive differences in the rise and the decline of plasma zolpidem concentrations when the proportion of extended release is increased. Though not displayed in Figure 2, the predicted plasma profile for the fastest releasing Formulation C is expected to have

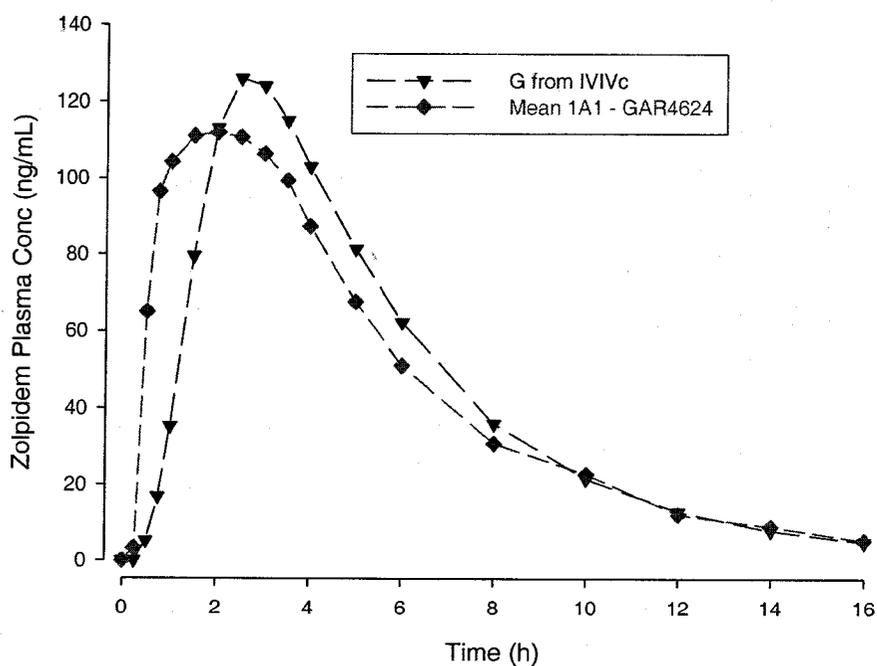
<sup>20</sup> Relative and absolute bioavailability of new zolpidem oral formulations (biphasic tablet) compared to Stilnox and injectable zolpidem, following single administration to normal young male subjects. Open, randomized, crossover and single center study; *published in* E. Weinling, et. al, "Pharmacokinetic Profile of a New Modified Release Formulation of Zolpidem Designed to Improve Sleep Maintenance. *Fundamentals of Clinical Pharmacology*. 2006 Aug; 20(4):397-403.

May 16, 2007

Page 10

a higher C<sub>max</sub> and be shifted left on the time scale of the plasma concentration-time curve compared to the marketed AMBIEN CR formulation.<sup>21</sup>

**Figure 2. Predicted Plasma Concentration - Time Profile Based on IVIVC for Slow Releasing Formulation G and Mean In Vivo Plasma Concentration Time Profile for Phase III AMBIEN CR Formulation from Study GAR4624<sup>22</sup>**



<sup>21</sup> As customary with rapidly releasing formulations, AMBIEN CR's IVIVC is not applicable for Formulation C.

<sup>22</sup> Intermediate releasing Formulation E, formulation 1A1 (included in GAR4624, the pivotal Phase III clinical trial and the pivotal bioequivalence trial) and formulation 2C3 (marketed AMBIEN CR) contain identical ratios of immediate and extended-release zolpidem and exhibit the intermediate in vitro release profile as shown in Figure 1 but have very slight differences in non-rate controlling excipients.

Using the projected plasma concentration data from the IVIVC for the slow releasing 12.5 mg Formulation G and the actual plasma concentration data from the clinical pharmacokinetic trial (GAR4624) of the formulation containing the proportions of IR and ER zolpidem chosen for marketing, it is possible to calculate and compare the pharmacokinetic parameters C<sub>max</sub> and AUC, as well as other parameters. Such a comparison reveals that despite these differently shaped plasma concentration time curves, the differences in proportions of IR and ER zolpidem had no substantive effect on the total area under the concentration time curves (AUC) and C<sub>max</sub> (Table 1a). Calculation of the 90% confidence intervals for these two parameters indicated that the AUC and C<sub>max</sub> would meet the Agency's bioequivalence criteria (Table 1b). Bioequivalence demonstrated through AUC and C<sub>max</sub> did not, however, predict an equivalent safety and efficacy profile.

**Table 1a. Pharmacokinetic Parameters of Slow Releasing 12.5 mg Formulation G and Intermediate Releasing Formulation 1A1<sup>#</sup> (mean of 24 subjects from GAR4624)**

Parameter	Formulation 1A1 (arithmetic mean)	Formulation 1A1 (geometric mean)	Formulation G**
C <sub>max</sub> (ng/mL)	134	130	126
AUC (ng*h/mL)	740	685	732
AUC <sub>0-3h</sub> (ng*h/mL)	274	261	209
AUC <sub>3-6h</sub> (ng*h/mL)	235	219	278
AUC <sub>6-∞</sub> (ng*h/mL)	232	191	245

<sup>#</sup> Formulation 1A1 and Formulation E were comparable formulations containing identical ratios of IR to ER

\*\*Pharmacokinetic parameters calculated from the concentration-time profile derived from the IVIVC (see Appendix A).

**Table 1b. Ratios (geometric mean) and 90% Confidence Intervals for the Pharmacokinetic Parameters for Formulation G\*\* (slow releasing) vs. Formulation E<sup>#</sup> (1A1, intermediate releasing) estimated with n=72 subjects**

Parameter	Point estimate	90%CI lower	90%CI upper
C <sub>max</sub>	0.97	0.91	1.04
AUC	1.07	1.00	1.14
AUC <sub>0-3h</sub>	0.80	0.73	0.88
AUC <sub>3-6h</sub>	1.27	1.17	1.37
AUC <sub>6-∞</sub>	1.28	1.14	1.44

<sup>#</sup> Formulation 1A1 and Formulation E were comparable formulations containing identical ratios of IR to ER

\*\*Pharmacokinetic parameters calculated from the concentration-time profile derived from the IVIVC (see Appendix A).

When the formulations with different proportions of IR and ER zolpidem were tested in the clinical pharmacology study PDY4054<sup>23</sup> using a sleep disturbance model,<sup>24</sup> the three different 12.5 mg formulations<sup>25</sup> produced differences in pharmacodynamic responses reflective of efficacy (Table 2) that were consistent with the differences in the measured dissolution rates and projected plasma concentrations. For example, when compared to placebo in the noise model study, the two 12.5 mg formulations with the most rapid release (the fast releasing formulation, referred to in Study PDY4054 as Formulation C and the intermediate releasing formulation, referred to in the study as Formulation E) significantly reduced sleep onset latency or awakenings during the first hour after falling asleep. The formulation with the slower initial release (referred to in Study PDY4054 as Formulation G), failed to promote sleep during the earliest part of the nighttime sleep period. During the middle of the night (4-5 hours after falling asleep), those formulations (E and G) that showed a later release of drug (and greater plasma concentrations during this portion of the night) showed reduced awakenings. At the tail end of the sleep cycle, the formulation (G) with the greatest predicted plasma concentration during the last 4 hours of the 8-hour sleep cycle produced significantly fewer minutes awake prior to the official waking time. This effect to sustain sleep late in the sleep cycle was, however, accompanied by an increase in impairment of cognition after waking.

---

<sup>23</sup> Double-blind, placebo-controlled, 10-way cross-over study comparing the pharmacodynamic effects of eight galenic formulations of zolpidem versus current marketed immediate release form of zolpidem, in healthy subjects.; *published in* Stanley N, Hindmarch I, Legangneux E, et al. Zolpidem modified-release 12.5 mg improves measures of sleep continuity in a model of sleep disturbance (traffic noise) compared with standard zolpidem 10 mg [abstract no, 321]. *Pharmacotherapy* 2005; 25(10): 1504. Plus oral presentation presented at the 2005 Annual Meeting of the American College of Clinical Pharmacy; 2005 Oct 23-26; San Francisco (CA). Moen MD, Plosker GL. Zolpidem Extended-release. *CNS Drugs*. 2006;20(5):419-426. Hindmarch I, Legangneux E, Emegbo, Dawson J, Stanley N. The effects of zolpidem extended-release versus placebo and original zolpidem on experimentally-induced sleep continuity disturbance. (Manuscript in preparation).

<sup>24</sup> This sleep disturbance model is a model that has been used to study hypnotic compounds and is intended to induce sleep difficulties in healthy volunteers.

<sup>25</sup> In Study PDY4054, the formulations were referenced by a single letter code. The fast releasing formulation is Formulation C, the intermediate releasing formulation is Formulation E, and the slow releasing formulation is Formulation G.

**Table 2. Summary Results for Key Sedative - Hypnotic Efficacy and Safety Parameters from Clinical Pharmacology Study - PDY4054**

	Mean value			
	Placebo	Formulation C (Fast release)	Formulation E <sup>#</sup> (Intermediate release)	Formulation G (Slow release)
Sleep onset latency (min)	12.86	9.00*	12.03	12.69
Awakenings during hr 1			Sig. < placebo*	
Awakenings during hr 2		Sig. < placebo*	Sig. < placebo*	Sig. < placebo*
Awakenings during hr 3		Sig. < placebo*	Sig. < placebo*	Sig. < placebo*
Awakenings during hr 4			Sig. < placebo*	
Awakenings during hr 5			Sig. < placebo*	Sig. < placebo*
Time awake 4 hr prior to lights on (min)	13.17	11.73	9.66	7.23*
Digit Symbol Substitution (number completed at 9 hours after dosing; approx. 1 hour after waking)	85.53	83.20	83.32	81.35*

<sup>#</sup> Marketed AMBIEN CR (see footnote 22)

\* Significantly different than placebo, P < 0.05

In addition, the different formulations produced differences in residual effects on cognition at 9 hours post dosing (after 7-8 hours of sleep). Of the 12.5 mg formulations C, E and G in study PDY4054, only the formulation with the slowest absorption rate, G, resulted in a significantly lower DSST score than placebo (Table 2).

Thus, release of drug by a formulation too early after administration limited its ability to maintain sleep during the middle of the night. Release of too large a proportion of drug later during the sleep cycle reduced effectiveness during the early portion of the night and resulted in psychomotor impairment for a period after awakening. As seen in Figure 2, the differences in effectiveness and safety occurred with relatively small differences in absolute plasma concentrations during that period. As stated by Tozer et al (1996), "the goal of bioequivalence trials should be to assure that the shape of the concentration-time curve of the test product is sufficiently similar to that of the reference product."<sup>26</sup>

<sup>26</sup> T.N. Tozer et al. Absorption Rate vs. Exposure: Which Is More Useful for Bioequivalence Testing?, Pharm Res., Vol. 13, No. 3, 1996, 453-456.

May 16, 2007

Page 14

**For extended-release sedative hypnotics, a comparison of only  $C_{max}$  and AUC is unlikely to adequately predict the pharmacodynamic impact of differences in plasma drug concentrations**

The pharmacodynamic impact of differences in plasma drug concentrations is unlikely to be adequately predicted by comparing only the  $C_{max}$  and AUC of generic products with AMBIEN CR. As opposed to an immediate-release formulation of zolpidem with the same total dose as the innovator product, the timing of release is crucial to the efficacy and safety of an extended-release hypnotic.  $C_{max}$  and AUC do not totally characterize the complete time vs. concentration profile of a drug and therefore are ineffective in predicting potential safety and efficacy differences for a formulation that is highly time dependent on attainment, maintenance and disappearance of drug levels. Instead, additional parameters describing the entire time course of the plasma concentration curve should be compared.

As shown in Table 1a, the pharmacokinetic parameters of the slow release formulation (Formulation G) predicted based on IVIVC differ on several exposure assessments that define the plasma concentration profile of zolpidem over time.

The relative ineffectiveness of the slower releasing formulation (Formulation G) compared to the intermediate-release, Phase III AMBIEN CR formulation during the early period after falling asleep is reflected in the low ratio of the early exposure as measured by  $AUC_{0-3h}$  (Table 1b). The presence of cognitive impairment after waking (at 9 hours after dosing) for this formulation is reflected in the high ratios of plasma concentration compared to the intermediate-release Phase III AMBIEN CR formulation in the latter part of the night as measured by  $AUC_{6-\infty}$ .

Generic formulations that have more rapid dissolution and drug release properties than AMBIEN CR may suffer from a relative ineffectiveness during the middle of the night (like Formulation C). Similarly, given the predicted plasma concentration-time profile displayed in Figure 2, generic formulations that have slower dissolution and drug release properties than AMBIEN CR may suffer from relative ineffectiveness during the early part of the sleep cycle and may provide a greater potential for cognitive impairment after 7-8 hours of sleep, as shown for Formulation G. As the previous research has revealed, these differences in pharmacodynamic profiles may not be apparent based only on a comparison of  $C_{max}$  and AUC. However, other pharmacokinetic parameters such as  $AUC_{0-3h}$ ,  $AUC_{3-6h}$ , and  $AUC_{6-\infty}$ , may be more sensitive in differentiating therapeutically equivalent zolpidem extended release formulations from those that are not. Not surprisingly, in sanofi-aventis' pivotal bioequivalence study (BDR5478<sup>27</sup>) comparing the plasma concentration time curves obtained in clinical

---

<sup>27</sup> See excerpt of BDR5478, Relative bioavailability study comparing a new tablet formulation (MRbis) of zolpidem and the reference tablet formulation (MR) at 12.5 mg after single oral (continued...)

May 16, 2007

Page 15

pharmacokinetic trials from the formulation tested in the pivotal Phase III clinical efficacy and safety trial to the marketed AMBIEN CR formulation, all of the aforementioned parameters were within  $\pm 20\%$  and met the strict bioequivalence criteria as detailed in the table below and had virtually superimposable plasma concentration curves as shown in the figure below:

**Table 3a. Pharmacokinetic Parameters (geometric mean) of Pivotal Phase III Formulation 1A1 and Marketed AMBIEN CR Formulation 2C3 (mean of 71 subjects from BDR5478) #**

Parameter	Formulation 1A1 <sup>28</sup>	Formulation 2C3
Cmax (ng/mL)	120	122
AUC (ng*h/mL)	624	615
AUC <sub>0-3h</sub> (ng*h/mL)	210	227
AUC <sub>3-6h</sub> (ng*h/mL)	207	201
AUC <sub>6-∞</sub> (ng*h/mL)	165	154

# 72 subjects participated in study BDR5478. Subject #44, who vomited in period 1 after formulation 2C3, was excluded from both periods for the calculations of point estimates and 90% CI, whereas in the study report, this subject was only excluded from period 1 and kept in period 2.

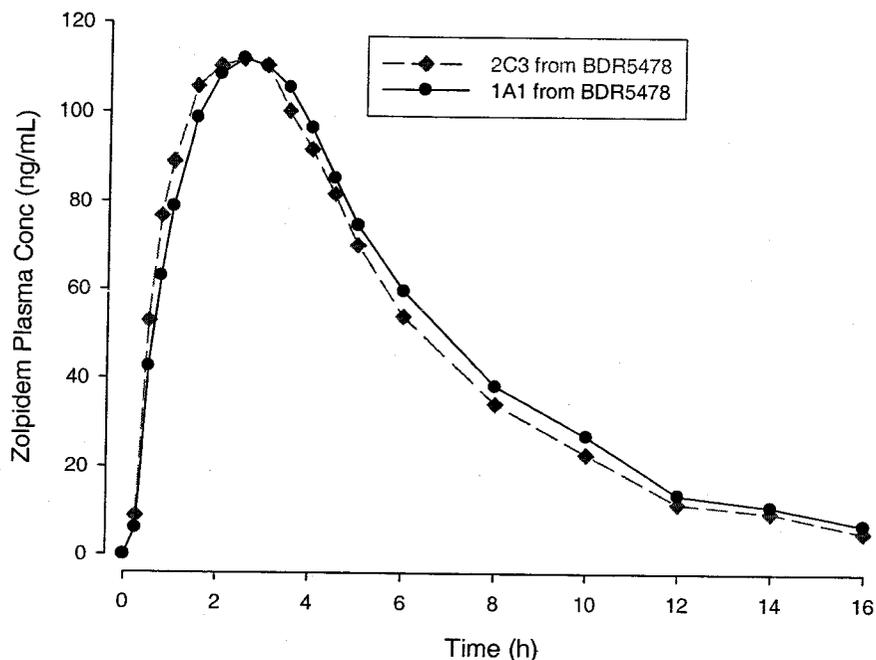
**Table 3b. Ratios (geometric mean) and 90% CI of pharmacokinetic parameters between the formulation shown in clinical trials to have optimal efficacy and safety and the marketed AMBIEN CR formulation (Study BDR5478; n=71 subjects)**

Parameter	Point estimate	90%CI lower	90%CI upper
Cmax	1.02	0.96	1.10
AUC	0.99	0.92	1.06
AUC <sub>0-3h</sub>	1.08	0.99	1.19
AUC <sub>3-6h</sub>	0.97	0.90	1.05
AUC <sub>6-∞</sub>	0.94	0.83	1.06

---

administration in healthy male and female subjects. Open, randomized, crossover and single center study in Appendix B.

<sup>28</sup> The pharmacokinetic parameters for Formulation 1A1 in Table 3a differ from those in Table 1a because different populations were used in the two studies. GAR4624 included 24 males only while BDR5478 included 72 males and females.

**Figure 3. Plasma concentrations of zolpidem from study BDR5478<sup>29</sup>**

#### IV. Conclusions

As demonstrated above, evaluation of only  $C_{max}$  and AUC parameters may fail to reveal differences in pharmacodynamic characteristics and therapeutic equivalence. In order to provide equivalent efficacy to marketed AMBIEN CR on sleep endpoints and minimal impairment of cognitive function after 7-8 hours asleep, sanofi-aventis requests that generic formulations be required to demonstrate a greater concurrence of plasma concentration-time curves than are reflected in just bioequivalent  $C_{max}$  and AUC values. Because the total plasma concentration-time profile of AMBIEN CR can be associated with three important qualities of sedative hypnotics -- time to sleep onset, maintenance of sleep, and lack of residual effects -- a generic of AMBIEN CR should be required to include an immediate release and extended-release component in the product to assure that the generic will have similar sleep induction and sleep maintenance capabilities and a similar safety profile, particularly upon awakening. In addition to the traditional FDA bioequivalence parameters ( $C_{max}$  and AUC), FDA should require generics to AMBIEN CR to demonstrate equivalence as a function of time such as  $AUC_{0-3h}$ ,  $AUC_{3-6h}$  and  $AUC_{6-\infty}$  to assure clinical equivalence.

<sup>29</sup> Formulations E, 2C3, and 1A1 all contain identical ratios of immediate and extended-release zolpidem and exhibit the intermediate in vitro release profile as shown in Figure 1.

May 16, 2007

Page 17

**V. Required Material**

**A. Environmental Impact**

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 & 25.31(a).

**B. Economic Impact**

An economic impact statement will be submitted at the request of the Commissioner.

**C. Certification**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Richard Gural, Ph.D

Vice-President, Regulatory Development

sanofi-aventis U.S. Inc.

9 Great Valley Parkway

Malvern, PA 19355

610-889-6632

Attachments