DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 19-908

Sanofi-Synthelabo Research
9 Great Valley Parkway
Malvern PA 19355

Attention: Daryl DeKarske, MPH
Director, Drug Regulatory Affairs

Dear Mr. DeKarske:

Reference is made to your March 31, 2005 Proposed Pediatric Study Request submitted to NDA 19-908 for Ambien (zolpidem tartrate) Tablets.

To obtain needed pediatric information on zolpidem tartrate, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from studies described below.

BACKGROUND

The study of insomnia in children may be complicated by the developmental changes in sleep requirements and sleep architecture that occur as a child grows from infancy to adolescence. Unlike the primary insomnia seen commonly in adults, insomnia in children is thought to be secondary to other conditions in most cases. While the list of conditions that may lead to secondary insomnia is under discussion by the sleep community, there is apparent agreement that the prevalence of insomnia complaints in children with attention-deficit, hyperactivity disorder (ADHD) and in children with neurodevelopmental disorders (NDD) appears higher than that of the general pediatric population.

Zolpidem tartrate, which is indicated for the short-term treatment of insomnia, has been shown to decrease sleep latency in adults, but there is incomplete information about dosing, effectiveness and safety in pediatric patients who receive zolpidem tartrate. The clinical study described in this written request would investigate the use of zolpidem tartrate for childhood insomnia in children with ADHD.

JUVENILE ANIMAL TOXICITY STUDIES

In order to provide additional safety information for labeling, you will need to conduct juvenile animal toxicity studies. These studies should utilize animals of an age range and stages of development that are comparable to the intended human population, and the animals should be exposed to the drug for a period that will cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, these studies should evaluate the effects of zolpidem tartrate on growth, reproductive development, and neurological and neurobehavioral development. Reproductive effects need to be evaluated following cessation of treatment; there should be a washout period of

appropriate duration (based on zolpidem's half-life) between cessation of treatment and evaluation. In assessing neurobehavioral development, the effects should be evaluated during treatment and after an appropriate washout period following the cessation of treatment (to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals should be used at the two assessment times. However, to avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects during treatment and the effects on reproductive parameters. The neurobehavioral tests should assess sensory function, motor function, and learning and memory. The neuropathological evaluation should include examination of all major brain regions and cellular elements, with particular attention to alterations indicative of developmental insult.

Protocols for juvenile toxicity studies should be submitted to the Division for comment prior to initiation. We acknowledge receipt of your submission of March 31, 2005 describing the juvenile toxicity study proposal. This submission is currently under review.

EFFICACY AND SAFETY STUDY

The study performed to fulfill this written request must be a randomized, placebo-controlled, double-blind, fixed-dose trial. We strongly recommend that the trial be a fixed dose study with doses that fully explore the dose range in this population (up to 0.25 mg/kg with a maximum dose of 10 mg). Dosing will be informed by the studies conducted by (or for) the company or data to which the company has right of reference. The dose characteristics (dose in mg/kg as well as mg per patient) should be recorded in the Case Report Form (CRF).

During screening, parents must be asked whether or not a trial of behavioral intervention has been tried and the duration of the trial if one was done. The responses are to be recorded in the CRF and reported as part of the background demographic data.

Prior to the issuance of this written request, a pharmacokinetics/pharmacodynamics study (Study L8749) was conducted and completed in 64 children aged 2 though 18 years. Certain information from that study may appropriately be used in the design of the study done to fulfill this written request.

Objective of Study

1. To evaluate the hypnotic efficacy and the safety of zolpidem in children with ADHD-associated insomnia

2. Determine whether there are next-day residual effects of zolpidem tartrate use in this patient population

Age Groups to be Studied

The study should enroll pediatric patients (of either gender) who are $\geq$ 6 years old to $\leq$ 17 years old.

Inclusion Criteria

- Male or female patients, ≥ 6 and ≤ 17 years old
- Children with ADHD as defined by DSM-IV criteria
- A complaint of childhood insomnia defined as repeated difficulty with sleep initiation or consolidation that occurs despite adequate age appropriate time (which must be defined within the protocol) and opportunity for sleep. The existence of sleep difficulty is supported by statements from the child and/or the caregiver that sleep is not properly initiated or maintained.
- Baseline Polysomnography (PSG) must reveal either > 30 minutes sleep latency (SOL) or >45 minutes wake after sleep onset (WASO).
- The sleep disturbance must not be attributable to either the direct physiologic effect of a drug of abuse or misuse of a prescribed medication.
- Subject should be stabilized on all long-term medication therapy for at least one month prior to study entry
- Subject should be using a recognized effective method of contraception excluding hormonal therapy. Abstinence is an acceptable method of contraception for this study.
- Written consent must be obtained from the parent/legal guardian
- Written assent must be obtained from pediatric patients of the appropriate age who are capable of giving assent as determined by parent/legal guardian. The process will be IRB approved.

Exclusion Criteria

- Mental retardation
- Autism spectrum disorder
- A history of sleep apnea
- Periodic limb movement > 5/hr as demonstrated on screening/baseline PSG
- Sleep-disordered breathing as demonstrated on screening/baseline PSG
- A history of bipolar disorder, major depression, conduct disorder, or generalized anxiety disorder (other than obsessive-compulsive disorder) as determined by clinical interview, Children's Depression Rating Scale and Pediatric Anxiety Rating Scale
- The presence of any untreated or uncompensated clinically significant renal, endocrine, gastrointestinal, hepatic, respiratory, cardiovascular, neurologic (excluding ADHD), hematological, immunologic, cerebrovascular disease or malignancy.
- Elevations in screening blood tests of renal and/or liver function > 2 times the upper limit of normal for age.
- Substance abuse or dependence
- Known hypersensitivity to zolpidem or previous adverse experience with zolpidem
- Pregnancy or lactation
- Use of any systemic contraceptive steroids including oral contraceptives, transdermal patch, vaginal insert, levonorgesterol implant and medroxyprogesterone acetate contraceptive injection
- Current use of antihistamines, melatonin, herbal products or other sleep aids including clonidine for initiation or maintenance of sleep and unwillingness to discontinue them at the screening visit
- Current participation in another clinical trial
- Subject's refrigerator is not large enough for a medication lock box

- Parent/guardian or subject is not capable of completing the study

Study Duration

Twelve weeks comprised of a screening/baseline phase of up to three weeks, an 8 week treatment phase, and a one week follow-up phase.

Number of Patients to be Studied or Power of the Study to be Achieved

A sufficient number of patients of both sexes to provide reasonable power (at least 80%) to detect a statistically significant difference in the primary efficacy endpoint must be studied. Pediatric patients must be approximately evenly distributed between sexes. There must also be approximately equal numbers of patients in the age groups ($\geq$ 6 to 11 years and 11 years to $\leq$ 17 years), reasonably distributed within the age ranges.

Efficacy Measures

The primary efficacy measure should be either PSG-determined latency to persistent sleep (for a sleep initiation indication) or PSG-determined wake time after sleep onset (for a sleep maintenance indication). The parameter that is not selected for the primary endpoint may be used as a key secondary endpoint.

Total sleep time will not be considered an acceptable primary endpoint.

The following parameters must also be investigated:
- Clinical Global Impression-parent/caregiver
- Clinical Global Impression-child
- Conner's ADHD rating scale

We will consider the results on these key secondary outcomes when evaluating the overall results of your trial.

The following parameters should also be investigated:
- PSG determined number of awakenings after sleep onset (NAASO)
- Actigraphic measures of sleep characteristics
- Behavioral variables
    - Pediatric Daytime sleepiness scale (PDSS)
    - Child behavioral checklist (CBCL)
    - School tardiness/attendance reports
    - Pediatric quality of life assessment (SF-10 for children)
- Cognitive variables
    - Conner's Continuous performance Test II (CPT-II)

Safety Measures

Adverse event data (based on spontaneous reports, physical examinations, and laboratory findings) must be collected.

Treatment residual effects will be assessed using the Pediatric Daytime sleepiness scale (PDSS)

Rebound insomnia is to be assessed after abrupt drug discontinuation via either PSG or actigraphic measures.

Your study must enroll enough patients so that safety data is collected for no fewer than 100 pediatric patients exposed to zolpidem for a minimum of 2 months.

Drug Information

- **Dosage form:** Use an age-appropriate formulation in the study described above. A liquid formulation of zolpidem tartrate, which may be flavored for palatability, would be acceptable.
- **Route of Administration:** Oral
- **Regimen:** Oral dosing once nightly
- If the study you conduct in response to this Written Request demonstrates that this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

  Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

  If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

  Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.
  If the formulation used in the PK and safety/efficacy studies is not the to-be-marketed formulation, a bioequivalence study may be required.

Labeling That May Result from the Study

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of Reports to be Submitted

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation must be submitted. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for Submitting Reports of the Study

Reports of the above studies must be submitted to the Agency on or before July 31, 2006. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a New Drug Application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have questions, call Cathleen Michaloski, BSN, MPH, Regulatory Project Manager, at 301-796-1123.

Sincerely,

{See appended electronic signature page}

Robert J. Temple, M.D.
Director
Office of Drug Evaluation One
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple

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