DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 21-476

Sepracor, Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

Attention: Amy LaForte, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. LaForte:

Reference is made to your October 18, 2005 Proposed Pediatric Study Request (PPSR) submitted to NDA 21-476 for Lunesta (eszopiclone) Tablets.

To obtain needed pediatric information on eszopiclone, 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 the four types of studies described below:

1) Juvenile Animal Toxicity Studies
2) Pharmacokinetic, Pharmacodynamic, and Tolerability Studies
3) Efficacy and Safety Study
4) Long-term Safety Study

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 goes from infancy to adolescence. Unlike primary insomnia seen in adults, insomnia in children is thought to be secondary to other conditions. 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.

Eszopiclone, which is indicated for the short-term and chronic treatment of insomnia, has been shown to decrease sleep latency in adults. However, there is incomplete information about eszopiclone dosing, effectiveness and safety in pediatric patients. The clinical studies described in this letter investigate the use of eszopiclone for childhood insomnia in children with ADHD.

1. Juvenile Animal Toxicity Studies

To provide additional safety information for labeling, you must conduct juvenile animal toxicity studies in two species (rodent and nonrodent) prior to conducting the clinical trials described below.

These studies must utilize animals of an age range and stage(s) of development that are comparable to the intended human population, and the animals must 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 must evaluate the effects of your drug on growth, reproductive development, and neurological and neurobehavioral development. The study design and the specific parameters assessed will depend to some extent on the species tested. Reproductive performance must be evaluated (typically in rodent) following cessation of treatment; there must be a washout period of appropriate duration (based on the half-life) between cessation of treatment and evaluation. In assessing neurobehavioral development, the effects must 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 must 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 must assess sensory function, motor function, and learning and memory. The neuropathological evaluation must include examination of all major brain regions and cellular elements, with particular attention to alterations indicative of developmental insult.

We strongly encourage you to submit protocols for juvenile toxicity studies to the Division for comment prior to initiation.

2. <u>Pharmacokinetic, Pharmacodynamic and Tolerability Studies</u>

You must obtain pharmacokinetic (PK) and pharmacodynamic (PD) data to provide information pertinent to dosing of the study drug in the relevant pediatric population. Therefore, you must perform preliminary tolerability studies (in which PK data can be obtained) to fully explore the range of tolerated doses.

Age Groups to be Studied

Your PK studies must include patients in the following age groups:

I: ≥ 6 to < 12 years
II: ≥ 12 to < 18 years

Study Design

The PK data could come from traditional single-dose or multiple-dose PK studies that explore the range of tolerated doses based on age group. The study must enroll sufficient numbers of patients to characterize the PK parameters of eszopiclone and its metabolite desmethylzopiclone. These PK parameters must include T_{max}, $t_{1/2}$, C_{max}, AUC, C_{ss} (average steady-state concentration if multiple dosing), K_e (elimination rate constant), V_d/F (volume of distribution) and CL/F (apparent oral clearance). If any of the above PK parameters are not included, the protocol must provide adequate rationale for excluding the parameter(s).

Patients for PK evaluation must be representative of the larger study population with respect to age and gender. This PK study must be conducted first: the selection of age-appropriate doses for the subsequent efficacy study (see below) must be based on the results of this study. A draft guidance document on pediatric pharmacokinetic studies is available at (http://www.fda.gov/cder/guidance/1970dft.pdf).

If blood sampling is a limiting factor in the younger patients, population analysis using a combination of frequent and sparse sampling from different studies (including the efficacy studies) may be performed for these age groups. If a sparse sampling approach is used, approximately 3-4 (and at least three) blood samples per subject in at least 3 time brackets covering the full concentration-time profile after the eszopiclone dose must be collected. Blood samples in population studies must not be collected at fixed time points. In addition, we suggest that a blood sample be collected as close in time as possible to the occurrence of serious adverse effects.

A guidance document on population pharmacokinetic studies is available at [www.fda.gov/cder/guidance/1852fnl.pdf].

Numbers to be Studied or Power of the Study to be Achieved

Sufficient numbers of patients must be studied to adequately characterize the pharmacokinetics and tolerability of eszopiclone within the specified age ranges. For a traditional PK/tolerability study, this would include at least 12 children per dose/group with a relatively uniform distribution of all ages and gender across the age ranges ($\geq$ 6 to < 12 and $\geq$12 to <18 years) to be evaluated. A larger number would be needed to perform sparse sampling than for traditional PK studies. A relatively uniform distribution of patients throughout the age range must be studied.

Study Endpoints

Pharmacokinetic parameters related to eszopiclone and its metabolite desmethylzopiclone including (but not limited to) AUC, half-life, C_{max}, T_{max}, apparent volume of distribution (V/F), and apparent oral clearance (CL/F) must be determined and other metrics as appropriate must be calculated, for each analyte. Subgroup analyses (or a population analysis) to evaluate the effect of various covariates, including gender, body weight, and body surface area, on exposure must be included.

The study must assess the following pharmacodynamic (PD) measures: time to sleep, total sleep time (TST), duration of sleep period, sleep efficiency, frequency of shifts between sleep stages, number and duration of awakenings, sleep onset latency, REM latency, slow wave sleep (SWS) latency, sleep stages, and non-REM/REM cycle parameters. If any of these PD parameters are not included, the protocol must provide adequate rationale for excluding the parameter(s).

Statistical Information

Statistical information must include descriptive statistics of pharmacokinetic parameters for both eszopiclone and its metabolite desmethylzopiclone, and descriptive statistics for pharmacodynamic parameters. The results of the PK study in pediatrics must be compared to historical adult data conducted under similar conditions (e.g., fed or fasted, dosing).

3. <u>Efficacy and Safety Study</u>

The study performed to fulfill this written request must be a randomized, placebo-controlled, double-blind, fixed-dose trial. The study must include fixed doses that fully explore the tolerated dose range in this population (see above). 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) must be recorded in the case report form (CRF).

During screening, parents must be asked whether a trial of behavioral intervention has been tried and the duration of said trial if one was done. The responses are to be recorded in the CRF and reported as part of the background demographic data.

Objective of Study

The study objectives must include the following:

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

2. To evaluate whether there are next-day residual effects of eszopiclone use in this patient population

Age Groups to be Studied

The study must enroll pediatric patients (of either gender) who are ≥ 6 years old to <18 years old, i.e., school age.

Numbers 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 complete the studies. Pediatric patients must be approximately evenly distributed between sexes. There also must be approximately equal numbers of patients in the age groups (≥ 6 to < 12 years and ≥ 12 to < 18 years), reasonably distributed within the age ranges.

The study eligibility criteria must include the following inclusion criteria and exclusion criteria:

Inclusion Criteria (including, but not limited to:)

- Male or female patients, ≥ 6 and <18 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 onset 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.
- Patient must be stabilized on all long-term medication therapy for at least one month, and preferably for at least 3 months, prior to study entry.
- Written permission 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.

Exclusion Criteria (including, but not limited to:)

- 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
- Substance abuse or dependence
- Known hypersensitivity to eszopiclone or previous adverse experience with eszopiclone
- 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

Study Duration

The study must include at least 12 weeks of controlled treatment with eszopiclone.

Efficacy Measures

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

Total sleep time is not an acceptable primary endpoint.

You must assess the following parameters as key secondary outcomes:

- 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.

You must also assess the following parameters:

- 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

You must collect adverse events (based on spontaneous reports, physical examinations, and laboratory findings). Specific safety concerns include skin reactions and suicidality.

Monitoring must include baseline and end-of-study vital signs, weight and height measurements, clinical laboratory measures (including urinalysis, electrolytes, glucose, renal and liver function tests, and complete blood counts), and electrocardiograms (ECGs).

You must use the Pediatric Daytime sleepiness scale (PDSS) to assess treatment residual effects.

You must use either PSG or actigraphic measures to assess rebound insomnia after abrupt drug discontinuation.

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board (DSMB) with pre-specified study stopping rules shall be included in all studies.

4. <u>Long-term Safety Study</u>

You must collect safety data on at least 100 pediatric patients with ADHD exposed to eszopiclone for a minimum of 12 months. Patients must be approximately evenly distributed between sexes. There also must be approximately equal numbers of patients in the age groups ($\geq$ 6 to < 12 years and $\geq$ 12 to < 18 years), reasonably distributed within the age ranges.

The long-term safety data must be at or above the dose or doses identified as effective (for that age and indication). If an adequately designed and conducted effectiveness (see "Efficacy and Safety Study" above) trial fails to detect a drug effect, you must still conduct this long-term safety study, using doses at least as high as the highest dose administered in your pediatric "Efficacy and Safety Study" (see above).

We encourage you to perform this long-term safety study as an open-label extension study in which you roll over all patients after their fixed-dose controlled study of eszopiclone (see "Efficacy and Safety Study" above) for additional dosing through one year. You may supplement the enrollment of patients who complete the fixed-dose controlled study by enrolling children previously unexposed to eszopiclone, as long as they meet the entry criteria.

Safety outcome measures must include baseline and end-of-study vital signs, weight and height measurements, clinical laboratory measures (including urinalysis, electrolytes, glucose, renal and liver function tests, and complete blood counts), electrocardiograms (ECGs), and regular ascertainment of adverse events. Specific safety concerns include skin reactions and suicidality. Also, given recent concerns regarding possible induction of suicide with sedative/hypnotics, a more specific ascertainment for suicidality must be added to these trials.

Drug Information (applies to all clinical studies)

- **Dosage Form**

Use an age-appropriate formulation in the study(ies) described above. If the studies you conduct in response to this Written Request demonstrate 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 must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the appropriate formulation may be required in adults. You must submit full study reports of any relative bioavailability studies to the Agency along with the pediatric study reports.

- **Route of administration:** Oral

- **Regimen:** Oral dosing once nightly

Labeling that may result from the studies

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

Format of reports to be submitted

Timeframe for submitting reports of the studies

You must submit full study reports, not previously submitted to the Agency, addressing the issues outlined in this request with full analysis, assessment, and interpretation. 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(ies) 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.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/cder/guidance/6766fnl.pdf.

You must submit reports of the above studies to the Agency on or before September 15, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time of your submission.

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 must be submitted as a supplement to the approved NDA 21-476 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 (240-276-9327) 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 (e.g., pending or withdrawn after the supplement was filed);
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 must 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/). Although not required, we encourage you to register all trials for all diseases and conditions. 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 any questions, call Cathleen Michaloski, MPH, Regulatory Project Manager, at 301-796-1123.

Sincerely,

{See appended electronic signature page}

Robert J. Temple, M.D.
Director
Office of Drug Evaluation 1
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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