



NDA 22117

**REVISED WRITTEN REQUEST
AMENDMENT 3**

Organon USA Inc.
Attention: Irene Nunes, OD, PhD
Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY 33-204
Rahway, NJ 07065

Dear Dr. Nunes:

Please refer to your correspondence dated August 9, 2013, requesting changes to FDA's October 22, 2010 Written Request for pediatric studies for Saphris (asenapine) sublingual tablets.

We have reviewed your proposed changes and are amending the below-listed subsection of both the Pediatric Schizophrenia and Pediatric Bipolar Disorder sections of the Written Request. All other terms stated in our Written Request issued on September 23, 2009, and as amended on June 2, 2010, and October 22, 2010, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Number of Patients to be Studied

Pediatric Safety Study

This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or doses identified as effective in an adequately designed trial, or if this trial fails to detect a drug effect, at doses equivalent to the adult exposure of the drug. A combined total of at least 100 patients from the schizophrenia safety study and the bipolar safety study together, diagnosed with either schizophrenia or bipolar disorder and exposed to drug for at least 6 months, would be a minimum requirement for long-term safety.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated September 23, 2009, as amended by this letter and by previous amendments dated June 2, 2010, and October 22, 2010, must be submitted to the Agency on or before December 1, 2016, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, 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 IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact Sharonjit Sagoo, Pharm.D., Regulatory Project Manager, at sharonjit.sagoo@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended



**REVISED WRITTEN REQUEST
AMENDMENT #3**

NDA 022117

Organon USA Inc.
Attention: Irene Nunes, OD, PhD
Directory, Worldwide Regulatory Affairs
P.O. Box 2000, RY 33-204
Rahway, NJ 07065

Dear Dr. Nunes,

Please refer to your new drug application, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saphris (asenapine) Sublingual Tablets.

Please also refer to the Written Request for Pediatric Studies issued to you on September 23, 2009, the Revised Written Request (Amendment #1) issued to you on June 2, 2010, and the subsequent discussions regarding further proposed changes, including your September 29, 2010 agreement email. As agreed upon, the following constitutes the updated Written Request.

PEDIATRIC SCHIZOPHRENIA

General Advice for Developing a Drug for Pediatric Schizophrenia

Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1%. According to the DSM IV, the diagnostic criteria for schizophrenia are the same for the pediatric and adult populations, but the symptomatology and prevalence of schizophrenia in these two populations have been recognized to be somewhat different. Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults (APA Practice Parameters, 1997). Schizophrenia has also been described in children, but it is thought to be uncommon (AACAP Practice Parameters, 2001). Although there are not adequate epidemiological data, one author suggests that 0.1 to 1% of schizophrenic psychoses will present prior to age 10 (Remschmidt, 1996). In addition, the symptoms in childhood schizophrenia differ from those typically seen in adult schizophrenia and the diagnosis is more difficult to establish in this younger population (Volkmar, 1996).

Given the finding that childhood onset schizophrenia may present with symptoms quite different from those of adult onset schizophrenia, it would be important to systematically study the efficacy of

treatment within this pediatric population, ages 12 and under. The very low incidence of schizophrenia diagnosed prior to the age 13, however, makes it unlikely that it would be possible to conduct a sufficiently large study of this age group within a reasonable time. For this reason, and because there is still controversy about the validity of this diagnosis in children, this written request will be limited to the study of schizophrenia in adolescents aged 13 to 17 years.

Under current regulations [21 CFR 201.57(c)(9)(iv) in the 2009 CFR], a new claim in an adolescent population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity if it were believed that schizophrenia was essentially the same disease in adults and adolescent patients. Under FDAMA (1997), a claim might be based on a single study in adolescent patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the guidance document entitled "Guidance for Industry-Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach also requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in adolescent and adult populations to make data from the adult efficacy studies pertinent to adolescent patients. We believe that a sufficiently strong case has been made for continuity between adult and adolescent schizophrenia to permit an adolescent claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent schizophrenia. In addition, an adolescent schizophrenia program would need to include pharmacokinetic information and safety information in adolescents (13-17) with schizophrenia.

In issuing this request, we would like to stress the importance and challenge of accurately diagnosing schizophrenia in the pediatric population. The differential diagnosis may include bipolar disorder, mood disorder with psychosis, personality disorder, other psychotic disorders with organic etiologies, in addition to many disorders that classically present in childhood, such as the pervasive developmental disorders and developmental language disorders (AACAP Practice parameters, 2001). An indication of the difficulty of diagnosis is an NIMH study reporting that 7 of 31 (23%) children originally diagnosed with treatment-resistant childhood-onset schizophrenia were re-assessed after a 4 week medication free wash-out period and found not to have that disease; revised diagnoses included posttraumatic stress disorder, atypical psychosis, and personality disorder (Kumra, 1999).

Bibliography

American Academy of Child and Adolescent Psychiatry (2001). Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40(7, Supplement), 4S-23S.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

American Psychiatric Association (1997). Practice guideline for the treatment of patients with schizophrenia. *American Journal of Psychiatry*, 154(4 Suppl): 1-63.

Kumra, S, Briguglio C, Lenane M, et al. (1999), Including Children and Adolescents with Schizophrenia in Medication-Free Research. *American Journal of Psychiatry*, 156:7: 1065-1068.

Remschmidt H, Schulz E, Herpertz-Dahlmann B (1996), Schizophrenic Psychoses in Childhood and Adolescence *CNS Drugs* Aug; 6(2):100-112.

Volkmar F (1996), Childhood and Adolescent Psychosis: a Review of the Past 10 Years *Journal of the American Academy of Child and Adolescent Psychiatry* 35(7):843-851.

Specific Study Requirements for a Development Program in Adolescent Schizophrenia

Overall Objectives/Rationale

The overall goal of the development program should be to establish the safety and efficacy of asenapine sublingual tablets in the treatment of adolescent schizophrenia. This will require the development of other information, to include pharmacokinetic data, to support dosing recommendations in adolescent patients.

The required studies include:

Pediatric (ages 13-17 years) Pharmacokinetic and Tolerability Studies
Pediatric (ages 13-17 years) Efficacy and Safety Trial
Pediatric Safety Study

All of the clinical trials must be limited to patients capable of giving assent to participate in the trial.

Study Design

Pediatric Pharmacokinetic and Tolerability Study

You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in relevant pediatric populations. These data should come from a traditional pharmacokinetic study designed to determine appropriate dosing and the tolerability profile in relevant pediatric populations. This study should fully explore the range of tolerated doses and must be conducted before conducting the definitive efficacy and safety study. The selected dose(s) for study(ies) must be agreed upon with the Division prior to initiating the necessary pediatric efficacy and safety study(ies).

Pediatric Efficacy and Safety Trial

You must conduct a randomized, double-blind, parallel group, placebo-controlled trial in adolescent (ages 13-17 years) patients with schizophrenia, with a recommended duration of 6 to 8 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms worsen or are not adequately controlled on assigned treatment. At least 50% of patients assigned to active drug must complete to the nominal endpoint of this trial in order for it to be considered a completed trial and, therefore, responsive to this request. Complete information must be collected and provided for the reasons patients leave (drop out of) the trial. The trial must maximize the opportunity to detect a treatment effect of the drug in this population. Therefore, this trial must be of a fixed dose response design that includes doses that fully explore the tolerated dose range (established in the aforementioned pediatric pharmacokinetic and tolerability trial) in this population. In addition, given the concerns about placebo assignment to pediatric patients with schizophrenia, this study must have a Data Safety Monitoring Board to oversee its conduct in order to ensure that it is conducted safely.

Pediatric Safety Study

Safety data must be collected in the controlled efficacy trial. In addition, longer-term safety data, for a minimum duration of 6 months exposure to the drug, must be collected. The longer-term safety data could come from open studies, e.g., a longer-term open extension of the controlled efficacy trial populations or from separate longer-term open safety studies. Adequate longer-term safety data from studies in a single indication would be sufficient to meet this requirement. The long-term safety data must be at or above the dose or doses identified as effective in an adequately designed trial of efficacy,

as described above. If an adequately designed and conducted effectiveness trial fails to detect a drug effect, you must still collect long-term safety data, at doses equal to the adult exposure of the drug.

Age Group in Which Studies will be Performed –All Studies (Schizophrenia)

Adolescents diagnosed with schizophrenia (ages 13 to 17 years) must be included in the samples, and there must be a reasonable gender and age distribution within this sample.

Number of Patients to be Studied

Pediatric Pharmacokinetic and Tolerability Studies

We acknowledged you have completed a PK and tolerability study in 40 subjects, aged 12-17 years, and the study report has been previously submitted to the NDA. No additional PK and tolerability study is required.

Pediatric Efficacy and Safety Trial

The trial must have a sufficient number of patients to provide 85% statistical power to show a clinically meaningful difference between drug and placebo. It will likely be necessary to conduct a multicentered trial to ensure inclusion of a sufficient number of patients accurately diagnosed with schizophrenia. It may also be necessary to conduct an interim analysis to estimate variance late in the trial to increase the sample size if necessary to ensure that the trial has adequate power (see Statistical Information).

Pediatric Safety Study

This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or doses identified as effective in an adequately designed trial, or if this trial fails to detect a drug effect, at doses equivalent to the adult exposure of the drug. A combined total of at least 100 patients from the schizophrenia safety study and the bipolar disorder safety study together, diagnosed with either schizophrenia or bipolar disorder and exposed to drug for at least 6 months, would be a minimum requirement for long-term safety.

These studies must include reasonable representation of ethnic and racial minorities, i.e., the proportions of these groups in the studies should reasonably reflect proportions in the population. If you are not able to enroll adequate numbers of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Entry Criteria

These trials must include a valid and reliable diagnostic method for recruiting and enrolling newly diagnosed or poorly controlled adolescents meeting DSM-IV criteria for schizophrenia. Given the difficulty in making the diagnosis for screening purposes, a clinical interview of children and their parents or caregivers must be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also recommended that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Patient Evaluations and Study Endpoints

Pediatric Pharmacokinetic and Tolerability Studies

A pediatric pharmacokinetic and tolerability study in children ages 12 to 17 including those with schizophrenia, has been completed and the study report has been submitted to the NDA . No additional study is required.

Pediatric Efficacy and Safety Trial

A scale specific to schizophrenia and sensitive to the effects of drug treatment of schizophrenia in the target population must be used. The choice of the primary assessment instrument and the primary outcome will need to be justified. Specifically, if you choose scales and outcomes used in adult trials, you will need to justify that these measures are appropriate for use in the pediatric population. Alternatively, you may perform preliminary trials to identify sensitive rating scales in this population. It is essential to identify a primary outcome for the controlled efficacy trial; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial.

Pediatric Safety Study

Routine safety assessments must be collected at baseline and appropriate follow-up times, e.g., vital signs (pulse rate and blood pressure), weight, height, as measured by stadiometer, clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; serum lipids; and urinalysis), ECG's, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Given recent concerns regarding psychiatric adverse events with psychiatric medication use, particularly in children, you must provide an assessment of psychiatric adverse events (i.e. worsening of psychosis, depressed mood, suicidality and homicidal ideation) as part of this written request.

Suicidality Assessments in Clinical Studies

There has been much focus on treatment-emergent suicidality (suicidal ideation and behavior) in recent years, including the question of how best to assess for this in future trials. Given this development, the Division of Psychiatry Products (DPP) has developed a policy regarding how we will address this issue. All clinical protocols for products developed in DPP, whatever the indication, must include a prospective assessment for suicidality. These assessments would need to be included in every clinical protocol, at every planned visit, and in every phase of development. An acceptable instrument would be one that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The Columbia Suicide Severity Rating Scale (C-SSRS) would be an acceptable instrument. You can obtain information about the C-SSRS from Dr. Kelly Posner at Columbia University (posnerk@childpsych.columbia.edu).

You may propose alternatives, but you would then need to justify that the alternative instrument would meet this need, and you would need to obtain DPP's prior approval of the instrument. There will likely be several different approaches to administering the C-SSRS, including investigator administered or

self report (phone, computer, etc). Any approach could be acceptable as long as the method is validated.

There are two reasons for implementing this policy. One is to ensure that we collect better data on suicidality than we have up to now, so that in the future we will be able to conduct additional meta-analyses on this matter. A second reason is to ensure that patients in clinical trials who are experiencing suicidality are detected and adequately managed. This is important whether or not a particular drug is associated with treatment-emergent suicidality.

Statistical Information (Including Power of Studies and Statistical Assessments)

Pediatric Pharmacokinetic Study

A Pediatric pharmacokinetic study in children ages 12 to 17, including those with schizophrenia, has been completed.

Pediatric Efficacy and Safety Trial

This trial must have a detailed statistical plan. The trial should be designed with at least 85% statistical power to detect a clinically meaningful treatment effect (probably best based on typical effects in adults) at conventional levels ($\alpha=0.05$, 2-tailed) of statistical significance. A preliminary statistical analysis plan must be submitted for comment prior to initiating the efficacy and safety trial, and you must obtain agreement on the final statistical plan prior to 25% enrollment. Your study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. For the purpose of satisfying the Written Request, a clinically meaningful treatment benefit might, for example, be defined as an 8 unit difference between drug and placebo in change from baseline to endpoint on the PANSS total score.

This requires you to show that, if the true treatment effect for one of the treatment groups was "clinically meaningful", the pre-planned analysis would have at least 85% power to infer that at least one of the asenapine dose groups is significantly different from placebo. You may wish to obtain an estimate of variability to use in power calculations from a preliminary study. However, to ensure that the study is adequately powered, you must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. This interim analysis must be performed when the study is close to finishing (for example, at >90% of initially planned enrollment). Options for estimating variability are (1) a blinded, pooled analysis of all groups, or (2) a partially unblinded analysis of variability within each group (performed by an independent third party). No alpha-spending adjustment is required for this interim analysis to assess the variability, but if you want to perform an efficacy assessment at this or some other interim analysis, an appropriate alpha adjustment is required.

Pediatric Safety Study

A descriptive analysis of the safety data must be provided.

PEDIATRIC BIPOLAR DISORDER

General Advice for Developing a Drug for Mania and Mixed Episodes in Pediatric Bipolar Disorder

According to the DSM IV, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 10 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the 10 to 17 year-old population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in 10 to 17 year-olds should be feasible and should yield useful information.

Under current regulations [21 CFR 201.57(f)(9)(iv) in the 2008 CFR], a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity if it were believed that schizophrenia was essentially the same disease in adults and pediatric patients. Under FDAAA (2007), a claim might be based on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the draft guidance document entitled "Guidance for Industry-Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach also requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in pediatric and adult populations to make data from the adult efficacy studies pertinent to pediatric patients. We believe that a sufficiently strong case has been made for continuity between adult and pediatric bipolar disorder to permit a pediatric claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in pediatric bipolar disorder. In addition, a pediatric bipolar program would need to include pharmacokinetic information and safety information in pediatric patients in the 10-17 age range with bipolar disorder.

Bibliography

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

Specific Study Requirements for a Development Program in Pediatric Mania and Mixed Episodes in Bipolar Disorder

Objectives/Rationale

The overall goal of the development program should be to establish the safety and efficacy of asenapine sublingual tablets in the treatment of manic and mixed episodes in pediatric bipolar disorder.

This will require the development of other information, to include pharmacokinetic data, to support dosing recommendations in pediatric patients.

The required studies include:

Pediatric (ages 10-17 years) Pharmacokinetic and Tolerability Studies
Pediatric (ages 10-17 years) Efficacy and Safety Trial
Pediatric Safety Study

All of the clinical trials must be limited to patients capable of giving assent to participate in the trial.

Study Design

Pediatric Pharmacokinetic and Tolerability Study

You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in relevant pediatric populations. These data should come from a traditional pharmacokinetic study designed to determine appropriate dosing and the tolerability profile in relevant pediatric populations. This study should fully explore the range of tolerated doses and must be conducted before conducting the definitive efficacy and safety study in bipolar disorder. The selected dose(s) for study(ies) must be agreed upon with the Division prior to initiating the necessary pediatric efficacy and safety study(ies).

Pediatric Efficacy and Safety Study

You must conduct a randomized, double-blind, parallel group, placebo-controlled acute trial in pediatric (ages 10-17 years) patients with manic or mixed episodes of Bipolar I Disorder, with a recommended duration of at least 3 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms worsen or are not adequately controlled on assigned treatment. At least 50% of patients assigned to active drug must complete to the nominal endpoint of this trial in order for it to be considered a completed trial and, therefore, responsive to this request. Complete information must be collected and provided for the reasons patients leave (drop out of) the trial. The trial must maximize the opportunity to detect a treatment effect of the drug in this population. Therefore, this trial must be of a fixed dose response design that includes doses that fully explore the tolerated dose range (established in the aforementioned pediatric pharmacokinetic and tolerability trial) in this population. In addition, given the concerns about placebo assignment to pediatric patients with Bipolar I Disorder, this study must have a Data Safety Monitoring Board to oversee its conduct in order to ensure that it is conducted safely.

Pediatric Safety Trial

Safety data must be collected in the controlled efficacy trial. In addition, longer-term safety data, for a minimum duration of 6 months exposure to the drug, must be collected. The longer-term safety data could come from open studies, e.g., a longer-term open extension of the controlled efficacy trial populations or from separate longer-term open safety studies. Adequate longer-term safety data from studies in a single indication would be sufficient to meet this requirement. The long-term safety data must be at or above the dose or doses identified as effective in an adequately designed trial of efficacy, as described above. If an adequately designed and conducted effectiveness trial fails to detect a drug effect, you must still collect long-term safety data, at doses at least as high as the doses equal to the adult exposure of the drug.

Age Group in Which Studies will be Performed –All Studies (Bipolar I Disorder)

Pediatric patients (ages 10 to 17 years) diagnosed with manic or mixed episodes associated with bipolar disorder must be included in the sample, and there must be a reasonable gender and age distribution within this sample.

Number of Patients to be Studied

Pediatric Pharmacokinetic Study

We acknowledged that you have completed a PK and tolerability study in 40 subjects including those with schizophrenia, aged 12-17 years, and the study report has been previously submitted to the NDA. No additional study in this age group is required. However, because your clinical trials for bipolar disorder will enroll children ages 10 to 12 years old, you need to conduct a PK and tolerability study which focuses on the 10 to 12 year old age group. This study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for asenapine.

Pediatric Efficacy and Safety Study

The trial must have a sufficient number of patients to provide 85% statistical power to show a clinically meaningful difference between drug and placebo. It will likely be necessary to conduct a multicentered trial to ensure inclusion of a sufficient number of patients accurately diagnosed with manic or mixed episodes associated with bipolar disorder. It may also be necessary to conduct an interim analysis to estimate variance late in the trial to increase the sample size if necessary to ensure that the trial has adequate power (see Statistical Information).

Pediatric Safety Study

This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or doses identified as effective in an adequately designed trial, or if this trial fails to detect a drug effect, at doses equivalent to the adult exposure of the drug. A combined total of at least 100 patients from the schizophrenia safety study and the bipolar disorder safety study together, diagnosed with either schizophrenia or bipolar disorder and exposed to drug for at least 6 months, would be a minimum requirement for long-term safety.

These studies must include reasonable representation of ethnic and racial minorities, i.e., the proportions of these groups in the studies should reasonably reflect proportions in the population. If you are not able to enroll adequate numbers of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Entry Criteria

These trials must include a valid and reliable diagnostic method for recruiting and enrolling newly diagnosed or poorly controlled pediatric patients meeting DSM-IV criteria for manic or mixed episodes associated with bipolar disorder. Given the difficulty in making the diagnosis for screening purposes, a clinical interview of children and their parents or caregivers must be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also recommended that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Patient Evaluations and Study Endpoints

Pediatric Pharmacokinetic and Tolerability Studies

The study should determine the appropriate dose range for efficacy and tolerability in the pediatric population. This dose range must be defined prior to beginning the definitive efficacy and safety trial in bipolar disorder. Pharmacokinetic assessments must be made with respect to the study drug and any active metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each active metabolite measured, the data collected must provide adequate estimates of important pharmacokinetic parameters, e.g., AUC, half-life, C_{max}, T_{max}, and apparent oral (sublingual) clearance (this parameter for parent only) in pediatric patients in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacology (Draft)].

Pediatric Efficacy and Safety Study

A scale specific to mania and sensitive to the effects of drug treatment on mania and mixed episodes of bipolar disorder in the target population should be used. The choice of the primary assessment instrument and the primary outcome will need to be justified. Specifically, if you choose scales and outcomes used in adult studies, you will need to justify that these measures are appropriate for use in the pediatric population. Alternatively, you may perform preliminary trials to identify sensitive rating scales in this population. Justification of primary endpoint selection will be of particular concern if the definitive effectiveness trial fails to distinguish drug from placebo. It is essential to identify a primary outcome for the controlled efficacy trial; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial.

Pediatric Safety Study

Routine safety assessments must be collected at baseline and appropriate follow-up times, e.g., vital signs (pulse rate and blood pressure), weight, height, as measured by stadiometer, clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; serum lipids; and urinalysis), ECG's, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Given recent concerns regarding psychiatric adverse events with psychiatric medication use, particularly in children, you must provide an assessment of psychiatric adverse events (i.e. worsening of psychosis, depressed mood, suicidality and homicidal ideation) as part of this written request.

Suicidality Assessments in Clinical Studies

There has been much focus on treatment-emergent suicidality (suicidal ideation and behavior) in recent years, including the question of how best to assess for this in future trials. Given this development, the Division of Psychiatry Products (DPP) has developed a policy regarding how we will address this issue. All clinical protocols for products developed in DPP, whatever the indication, must include a prospective assessment for suicidality. These assessments would need to be included in every clinical protocol, at every planned visit, and in every phase of development. An acceptable instrument would be one that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The Columbia Suicide Severity Rating Scale (C-SSRS) would be an acceptable

instrument. You can obtain information about the C-SSRS from Dr. Kelly Posner at Columbia University (posnerk@childpsych.columbia.edu).

You may propose alternatives, but you would then need to justify that the alternative instrument would meet this need, and you would need to obtain DPP's prior approval of the instrument. There will likely be several different approaches to administering the C-SSRS, including investigator administered or self report (phone, computer, etc). Any approach could be acceptable as long as the method is validated.

There are two reasons for implementing this policy. One is to ensure that we collect better data on suicidality than we have up to now, so that in the future we will be able to conduct additional meta-analyses on this matter. A second reason is to ensure that patients in clinical trials who are experiencing suicidality are detected and adequately managed. This is important whether or not a particular drug is associated with treatment-emergent suicidality.

Statistical Information (Including Power of Studies and Statistical Assessments)

Pediatric Pharmacokinetic Study

Descriptive analysis of the pharmacokinetic parameters must be provided.

Pediatric Efficacy and Safety Study

This trial must have a detailed statistical plan. The trial should be designed with at least 85% statistical power to detect a clinically meaningful treatment effect (probably best based on typical effects in adults) at conventional levels ($\alpha=0.05$, 2-tailed) of statistical significance. A preliminary statistical analysis plan must be submitted for comment prior to initiating the efficacy and safety trial, and you must obtain agreement on the final statistical plan prior to 25% enrollment. Your study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. For the purpose of satisfying the Written Request, a clinically meaningful treatment benefit might, for example, be defined as a 5 unit difference between drug and placebo in change from baseline to endpoint on the YMRS.

This requires you to show that, if the true treatment effect for one of the treatment groups was "clinically meaningful", the pre-planned analysis would have at least 85% power to infer that at least one of the asenapine dose groups is significantly different from placebo. You may wish to obtain an estimate of variability to use in power calculations from a preliminary study. However, to ensure that the study is adequately powered, you must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. This interim analysis must be performed when the study is close to finishing (for example, at >90% of initially planned enrollment). Options for estimating variability are (1) a blinded, pooled analysis of all groups, or (2) a partially unblinded analysis of variability within each group (performed by an independent third party). No alpha-spending adjustment is required for this interim analysis to assess the variability, but if you want to perform an efficacy assessment at this or some other interim analysis, an appropriate alpha adjustment is required.

Pediatric Safety Study

Descriptive analysis of the safety data must be provided.

GENERAL REQUIREMENTS AND COMMENTS

Drug Information (Dosage Form, Route of Administration, Regimen)

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

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. Under these circumstances, 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 labeling 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 age appropriate formulation may be conducted in adults.

Drug Specific Safety Concerns

In each of the pediatric studies, you must adequately assess the following safety concerns that were identified in the adult schizophrenia asenapine program: hyperglycemia, leucopenia/neutropenia/agranulocytosis, orthostatic hypotension/bradycardia/syncope, QTc prolongation, akathisia and other extrapyramidal symptoms, weight gain, and somnolence.

Labeling That May Result from the Studies

You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that asenapine is safe and effective,

or whether such study results are inconclusive in the studied pediatric populations or subpopulations, the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies

Format of Reports to be Submitted

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies 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, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

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.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/7087rev.htm>.

Timeframe for submitting reports of the study(ies)

Reports of the above studies must be submitted to the Agency on or before May 13, 2015. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not

possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

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.

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 are 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 to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 301-276-9310.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. 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, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/cder/pediatric/index.htm>

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.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, contact Sharonjit Sagoo, Pharm.D., Regulatory Project Manager at sharonjit.sagoo@fda.hhs.gov.

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
08/30/2013