DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

WRITTEN REQUEST

NDA 200603

Sunovion Pharmaceuticals Inc.
Attention: Claudia Hernandez, MBA
Associated Director, Regulatory Affairs
One Bridge Plaza, Suite 150
Fort Lee, NJ 07024

Dear Ms. Hernandez,

Please refer to your new drug application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Latuda (lurasidone) oral tablets.

Reference is made to your Proposed Pediatric Study Request submitted to IND 61,292 for Latuda (lurasidone) oral tablets on July 7, 2011, requesting issuance of a Written Request to conduct pediatric studies to qualify for exclusivity under section 505A of the Act.

To obtain needed pediatric information on lurasidone, 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 trials in pediatric patients with schizophrenia and autistic disorder as described below.

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-TR, 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.[1] 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.[2] Schizophrenia has also been described in children, but it is

[1] American Psychiatric Association (2000), Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association.

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

thought to be uncommon.[3] Although there are not adequate epidemiological data, one author suggests that 0.1 to 1% of schizophrenic psychoses will present prior to age 10.[4] 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.[5]

Given the finding that childhood onset schizophrenia may present with symptoms quite different from those of adult onset schizophrenia, it would be important to study systematically 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 FDAAA (2007), 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" (1998). 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 (ages 13-17) with schizophrenia.

A well-controlled clinical trial is one that includes a placebo arm in order to determine the efficacy of the antipsychotic medication.[6,7] To minimize risk for patients with schizophrenia in either arm(s) of a clinical trial, the study design should include rescue medications to treat acute clinical symptoms as well as discontinuation criteria. These clinical trials should also include an adequate washout period for discontinuation of medications (e.g. antipsychotics) prior to randomization. In some cases, washout periods may be beneficial if diagnoses change based on clinical reevaluation of patients prior to randomization.[8]

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3 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

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

5 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

6 Kemp AS, Schooler NR, Kalali AH et al (2010) What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophrenia Bull 36(3):504-9

7 Laughren TP (2001) The scientific and ethical basis for placebo-controlled trials in depression and schizophrenia: an FDA perspective Eur Psychiatry Nov 16(7);418-23

8 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

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.[3] 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.[8]

Specific Study Requirements for a Development Program in Adolescent Schizophrenia

Overall Objectives/Rationale

The overall goal of the development program is to establish the safety and efficacy of lurasidone 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 Study
- Pediatric (ages 13-17 years) Efficacy and Safety Study
- 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 the relevant pediatric population. These data should come from a traditional pharmacokinetic study designed to determine appropriate dosing and the tolerability profile in the relevant pediatric population. This study should fully explore the range of tolerated doses and must be conducted before designing and 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 study(ies).

Pediatric Efficacy and Safety Study

You must conduct a randomized, double-blind, parallel group, placebo-controlled study in adolescent (ages 13-17 years) patients with schizophrenia, with a recommended duration of 6 weeks. It is recommended that this study include an active comparator antipsychotic drug arm in addition to a placebo arm. The study 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 study 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 study 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.

You are required to use lurasidone pediatric pharmacokinetic data to inform your dosing strategy in the trial. The study should allow a characterization of potential-dose response or exposure-response relationships to inform labeling recommendations on dosing. We recommend that you perform pharmacometrics-based modeling and simulation to inform the study design. Specifically, we recommend that you conduct a dose (or exposure)-response analysis in adolescent patients, taking into account the time course of the rating scale used as the primary efficacy variable scores under the proposed design. You must obtain agreement from the FDA on the resultant study design prior to initiating the study.

Pediatric Safety Study

Safety data must be collected in the controlled efficacy study. 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-label studies, e.g., a longer-term open extension of the controlled efficacy trial populations or from separate longer-term open-label safety studies. 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 Study

A sufficient number of patients to adequately characterize the appropriate dose range, tolerability, and pharmacokinetics of the study drug and its major active metabolite(s) in the relevant age group must be studied. The full spectrum of age strata in the 13-17 year old continuum must be represented (e.g., 13-15, 16-17). The study must be prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for lurasidone in the entire age range (13-17 years of age). You must perform a preliminary tolerability study to fully explore the range of tolerated doses before designing and conducting the definitive efficacy and safety trial.

Pediatric Efficacy and Safety Study

The study must have a sufficient number of patients to provide at least 85% statistical power to detect a clinically meaningful difference between drug and placebo. It will likely be necessary to conduct a multicenter trial to ensure inclusion of a sufficient number of patients accurately diagnosed with

schizophrenia. You must 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. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety. The long-term safety data can be obtained from both the schizophrenia and autism trials combined, i.e., it is not necessary to obtain safety data for 100 patients for each population (see Autism (Autistic Disorder) section of Written Request).

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 disease 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 studies must include a valid and reliable diagnostic method for recruiting and enrolling newly diagnosed or poorly controlled adolescents meeting DSM-IV-TR 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.

Study Endpoints

Pediatric Pharmacokinetic and Tolerability Study

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 study. 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 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072114.pdf.

You must obtain agreement from the FDA on the pharmacokinetic (PK) sampling scheme. We recommend that you conduct an exposure-response analysis for both effectiveness and key safety variables.

Pediatric Efficacy and Safety Study

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 study; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your 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; glucose; and urinalysis), ECGs, 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, suicidal ideation/behavior and homicidal ideation) as part of this written request.

Pediatric Safety Study

The routine safety assessments including assessment of psychiatric adverse events as stated in the above paragraph under the Efficacy and Safety Study section must be collected in this pediatric safety study as well.

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 at http://www.cssrs.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 PK parameters must be provided.

Pediatric Efficacy and Safety Study

This study must have a detailed statistical plan. A preliminary statistical analysis plan must be submitted for comment prior to initiating the efficacy and safety study, and you must obtain agreement on the final statistical plan prior to 25% enrollment.

The study must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect (probably best based on typical effects in adults) at a Type I error rate of 0.05 (two-sided). You must obtain agreement with the Division with regard to the treatment effect prior to initiating the study. For the purpose of satisfying the Written Request, this treatment effect might, for example, be defined as a 5-unit difference between drug and placebo in change from baseline on the PANSS total score.

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.

AUTISM (AUTISTIC DISORDER)

General Advice for Developing a Drug for Irritability Associated with Autistic Disorder

Autism is a neuro-developmental disorder characterized by impairments in social interactions, communication, and restricted interests and stereotyped behaviors. Autistic disorder, or "classic" autism, is a more severe type of autistic spectrum disorder (ASD) that includes autistic disorder, Asperger's syndrome, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS).[1]

In 2006, the CDC estimated that an average of 1 in 110 children in the U.S. has an ASD.[7] The risk is 3–4 times higher in males than females. The number of children with ASDs has risen dramatically over the past decade (previously thought to be about 4 to 5 per 10,000 children) and has resulted in a public health concern. The reasons for this increase are not well understood. Some of the reported increases are attributed to new administrative classifications in special-education settings and the reclassification of children from a different category to autism; and the early detection of at risk children, prior to age of 3 years, to allow for early intervention services. However, environmental factors and gene-environment interactions, including epigenetic factors, are also thought to play a role.

In autistic disorder and ASD, many comorbid symptoms co-exist, including cognitive and intellectual disabilities, language deficits, motor abnormalities, attentional difficulties, hyperactivity, affective difficulties (e.g., anxiety and depression), interfering repetitive activity, irritability, aggression, self-

injurious behavior, and sleep disruptions. These comorbid symptoms can have significant impact on a patient's quality of life and therapies that target these symptoms could be beneficial to these patients.

Current Treatments for Irritability Associated with Autistic Disorder

There are currently no medications specifically approved in the US for the treatment of any of the three core domains of autism. Risperdal® (risperidone) and Abilify® (aripiprazole) are indicated for the treatment of irritability associated with autistic disorder in children and adolescents 5–17 years of age (6-17 years for aripiprazole, 5-16 years for risperidone), including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. It is likely that other antipsychotics, including lurasidone, will be used off-label for the treatment of irritability in children and adolescents with autistic disorder. Therefore, it is important to evaluate the efficacy and safety of other atypical antipsychotics in this patient population.

To obtain needed pediatric information on lurasidone, the FDA is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

Specific Study Requirements for Development Program in Irritability Associated with Autistic Disorder

The required studies include:

- Nonclinical Toxicology Study
- Pediatric (ages 6-17 years) Pharmacokinetic and Tolerability Study
- Pediatric (ages 6-17 years) Efficacy and Safety Study
- Pediatric (ages 6-17 years) Safety Study

Study Design

Nonclinical Toxicology Study

A juvenile animal study is required (b) (4) for use of lurasidone in 6-12 year-old patients diagnosed with irritability associated with autistic disorder and provide safety information for labeling. You may conduct this study concurrently with the Pediatric Pharmacokinetic and Tolerability Study because the traditional PK dose-ranging study is of short duration and would enroll a small number of pediatric subjects. However, this nonclinical toxicity study will need to be completed before exposing children 12 years old or younger in the subsequent, more expanded clinical efficacy and safety studies. The juvenile toxicity study should utilize animals of an age range and stage of development that are comparable to that of the intended human population, exposed to the drug for a duration that will cover the intended length of treatment in the pediatric population. In addition to the standard toxicological parameters, the study should evaluate the effects of lurasidone on growth, reproductive development, and neurological and neurobehavioral development. Reproductive effects should be assessed after cessation of treatment and there should be a washout period of appropriate duration (depending on the half-life of the drug) between the last dose of study drug and evaluation. For neurobehavioral development, effects should be assessed during treatment and following an appropriate washout period after cessation of treatment (to evaluate potential long-term

effects). To avoid confounding effects of repeated neurobehavioral testing, separate groups of animals should be used for each of the assessment times. However, in order to avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects and the effects on reproductive parameters. The neurobehavioral tests should assess sensory function, motor function, and learning and memory. Neuropathological evaluation should examine all major brain regions with emphasis on any alterations indicative of developmental injury.

Pediatric Pharmacokinetic and Tolerability Study

You must obtain PK data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data should come from a traditional PK study designed to determine appropriate dosing information and the tolerability profile in the relevant pediatric population. This study should fully explore the range of tolerated doses and must be conducted before designing and conducting the definitive efficacy and safety study. You must obtain agreement with the Division on dose selection for the study prior to initiating the necessary pediatric studies.

Pediatric Efficacy and Safety Study

As part of this Written Request, you must conduct one (1) randomized, double-blind, placebo-controlled study with a minimum duration of 6 weeks. The primary goal of this study would be to evaluate the efficacy and safety of lurasidone in the treatment of irritability associated with autistic disorder. In order to assess the potential dose-response and exposure-response relationships for effectiveness and tolerability, as well as to inform labeling recommendations on dosing, the study must include two fixed doses of lurasidone. At least 50% of subjects assigned to active drug must complete at least 6 weeks of treatment for the trial to be considered completed and, therefore, responsive to this request. Complete information about the reasons for subjects leaving the trial must be collected and provided**.** You must obtain agreement from the FDA on the study design prior to initiating the study.

Pediatric Safety Study

Also as part of this Written Request, you must collect safety data in the controlled efficacy study. You must collect longer-term safety data through a minimum of 6 months of drug exposure. The longer-term safety data could be derived from open-label studies, e.g., a longer-term open extension of the controlled efficacy trial populations, from separate longer-term open safety studies, or from controlled studies, e.g., a longer-term safety and efficacy trial. The long-term safety data must be obtained at or above the dose or doses identified as effective in an adequately designed trial, 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 typically used in treating patients with this drug.

We recommend that you submit the study protocol to the Division for comment prior to study initiation.

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

Children and adolescents ages 6 to 17 years must be included in the sample.

Representation of Ethnic and Racial Minorities

These studies must take into account adequate (e.g. proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Number of Patients to be Studied

Pediatric Pharmacokinetic and Tolerability Study

You must study a sufficient number of patients to characterize adequately the appropriate dose range, tolerability, and pharmacokinetics of lurasidone and its major active metabolite(s) in the relevant age group. One clinical trial that includes both patients with schizophrenia (13-17 years of age) and patients with autism (6-17 years of age) may be conducted to fulfill this request. The full age spectrum of age strata in the 6-17 year old continuum must be represented (e.g., 6-9, 10-12, 13-15, 16-17). The gender distribution of participants in these studies should reflect the distribution in those affected with these conditions. The 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 lurasidone in the 6-12 year and the 13-17 year age groups. You must perform a preliminary tolerability study to explore fully the range of tolerated doses before designing and conducting the definitive efficacy and safety study.

Pediatric Efficacy and Safety Study

The study must have a sufficient number of subjects to provide at least 85% statistical power to detect a difference between lurasidone and placebo on the symptom of irritability in autistic disorder. It will likely be necessary to conduct a multi-center study to ensure a sufficient population accurately diagnosed with autistic disorder. The irritability subscale of the Aberrant Behavior Checklist (ABC) would be acceptable as the primary efficacy measure. If you choose to use change from baseline in the irritability subscale of the ABC as the primary endpoint, the trial must be powered to show a 7-unit difference between drug and placebo. To ensure adequate statistical power in these studies, you must conduct an interim analysis to estimate variance late in the trials and increase the sample size if necessary (see Statistical Information).

Pediatric Safety Study

This study must include a sufficient number of pediatric patients to characterize adequately the safety of lurasidone 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. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety. The long-term safety data can be obtained from both the schizophrenia and autism trials combined, i.e., it is not necessary to obtain safety data for 100 patients for each population.

Entry Criteria

These studies must include a valid and reliable diagnostic method for recruiting and enrolling children and adolescents 6 – 17 years of age meeting DSM-IV-TR criteria for Autistic Disorder. A clinical interview of children and adolescents and their parents or caregivers must be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. Diagnosis should be confirmed by the Autism Diagnostic Interview-Revised**.**

Study Endpoints

Pediatric Pharmacokinetic and Tolerability Study

This 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 trials. Pharmacokinetic assessments must be made with respect to lurasidone 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 PK parameters, e.g., AUC, half-life, C_{max} , T_{max}, and apparent oral 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072114.pdf.

Pediatric Efficacy and Safety Study

Efficacy Endpoint

Although no rating scales have been validated specifically for the assessment of irritability in autistic disorder, an acceptable general scale for this assessment could include the irritability subscale of the Aberrant Behavior Checklist (ABC). Because autistic disorder is characterized by impairments in several aspects, e.g. social interactions, communication, and restricted interests and stereotyped behaviors, scales measuring other autistic core symptoms besides the domain covered by the primary efficacy measure should also be appropriately assessed.

Safety Endpoints

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; glucose and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Given recent concerns regarding psychiatric adverse events with psychiatric medication use, particularly in children and adolescents, you must provide an assessment of psychiatric adverse events as part of this written request.

Pediatric Safety Study

The routine safety assessments including assessment of psychiatric adverse events as stated in the above paragraph under the Efficacy and Safety Trial section must be collected in this pediatric safety study as well.

Statistical Information (Including Power of Studies and Statistical Assessments)

Pediatric Pharmacokinetic Study

Descriptive analysis of the PK parameters must be provided.

Pediatric Efficacy and Safety Study

The study must have a detailed statistical plan. A preliminary statistical analysis plan must be submitted for comment prior to initiating the efficacy and safety study, and you must obtain agreement on the final statistical plan prior to 25% enrollment.

The study must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect (probably best based on typical effects in adults) at a Type I error rate of 0.05 (two-sided). You must obtain agreement with the Division with regard to the treatment effect prior to initiating the study. For the purpose of satisfying the Written Request, this treatment effect might, for example, be defined as a 7-unit difference between lurasidone and placebo in change from baseline on the irritability subscale of the Aberrant Behavior Checklist.

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 completion (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.

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.

In accordance with section 505A(e)(2), 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 approval);
2. the Agency grants pediatric exclusivity, including publishing 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 indicating you have not marketed the new pediatric formulation.

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.

Known Drug Safety Concerns and Monitoring

In each of the pediatric studies, you must adequately assess the following safety concerns that were identified in the adult schizophrenia lurasidone program: extrapyramidal symptoms, hyperprolactinemia, somnolence, dizziness, angioedema/facial swelling and safety concerns associated with the use of atypical antipsychotic agents, such as QTc prolongation, orthostatic hypotension, leucopenia/neutropenia/agranulocytosis, weight gain, hyperglycemia, and dyslipidemia. Standard cut-off criteria for metabolic parameters (hyperglycemia and dyslipidemia) should be predefined in the protocols.

Extraordinary Results

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

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 lurasidone 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 and Types 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. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the postmarketing adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

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/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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/RegulatoryInformation/Guidances/ucm126959.htm.

Timeframe for Submitting Reports of the Studies

Reports of the above studies must be submitted to the Agency on or before December 30, 2016. 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 240-276-9327.

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, complete response); 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/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049872.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, please call Ann Sohn, Senior Regulatory Project Manager at 301-796-2232.

Sincerely yours,

{See appended electronic signature page}

Ellis Unger, M.D.
Acting Director
Office of Drug Evaluation I
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/

ELLIS F UNGER
04/20/2012