DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

IND 65,850, Cross Reference to (b) (4)

Johnson & Johnson Pharmaceutical Research & Development, LLC
Attention: Heddie Martynowicz, MS
Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms Martynowicz:

Reference is made to your Proposed Pediatric Study Requests submitted on April 28, 2006, to your Investigational New Drug Application (IND 65,850 and (b) (4) for paliperidone tablets.

To obtain needed pediatric information on paliperidone 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 as described below.

ADOLESCENT SCHIZOPHRENIA

General Advice for Developing a Drug for Adolescent-Onset 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. The very low incidence of schizophrenia diagnosed prior to the age 12, 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 12 to 17 years.

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 disorders, 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).

Under FDAMA, 1997, adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations. Although we are aware of only two published placebo controlled studies supporting the efficacy of neuroleptics (haloperidol & loxitane) in the treatment of pediatric schizophrenia (Spencer et al., 1992 & Pool et al., 1976), we believe that a sufficiently strong case has been made for continuity between adult and adolescent schizophrenia 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 adolescent schizophrenia. In addition, a pediatric schizophrenia program would need to include pharmacokinetic information and safety information in the relevant pediatric age group. For pediatric schizophrenia, we consider the relevant age group to include adolescents aged 12-17 years.

Finally, although we are requiring only certain specific studies, you will be expected to maximize the potential of the studies to demonstrate an effect of the drug in adolescents, if there is one. Toward this end, then, we urge you to perform additional studies (see below) in order to ensure that the required studies meet this goal.

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, 4 th 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.

Pool D, Bloom W, Mielke DH et al. (1976), A controlled evaluation of loxitane in seventy-five adolescent schizophrenia patients. Current Therapeutic Research Clinical and Experimental 19:99-104.

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

Spencer EK, Jafantaris V., Pardron-Gayol MV, et al. (1992), Haloperidol in schizophrenic children: early findings from a study in progress Psychopharmacol Bull 28:183-186.

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.

Nonclinical Toxicology Study

- A study in juvenile rats should be submitted prior to submission of the supplement. This study should utilize animals of an age range and stage(s) of development that are comparable to the intended human population, and the animals should be exposed to the drug for a period that will cover the intended length of treatment in the pediatric population. In addition to the usual

toxicological parameters, these studies should evaluate the effects of your drug on growth, reproductive development, and neurological and neurobehavioral development. Reproductive effects need to be evaluated following cessation of treatment; there should be a washout period of appropriate duration (depending on the half-life) between cessation of treatment and evaluation. In assessing neurobehavioral development, the effects should be evaluated during treatment and after an appropriate washout period following the cessation of treatment (to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals should be used at the two assessment times. However, to avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects during treatment and the effects on reproductive parameters. The neurobehavioral tests should assess sensory function, motor function, and learning and memory. The neuropathological evaluation should include examination of all major brain regions (b) (4), with particular attention to alterations indicative of developmental insult.

Protocols for juvenile toxicity studies should be submitted to the Division for comment prior to initiation.

Specific Study Requirements for Development Program in Adolescent Schizophrenia

Types of Studies

Pediatric Pharmacokinetic Study
Pediatric Efficacy and Safety Study
Pediatric Safety Study

Objective/Rationale

The overall goal of the development program would be to establish the safety and efficacy of the study drug in the treatment of adolescent schizophrenia, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Pharmacokinetic Study

- You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to preliminary efficacy trials or to other safety trials. You must perform preliminary tolerability studies (in which kinetic data can be obtained) to fully explore the range of tolerated doses, before conducting the definitive pharmacokinetic study and before conducting the definitive efficacy and safety studies. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Efficacy and Safety Study

- For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group,

placebo-controlled acute trial, with a recommended duration of at least 6 to 8 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. 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 on the reasons for patients leaving 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 fixed doses that fully explore the tolerated dose range in this population. In addition, we strongly recommend that you consider a relapse prevention trial to follow the acute treatment trial, in which responders, i.e. those patients who have been in a responder status for at least 3 months to acute treatment, would be randomized to study drug or placebo, with follow-up observation for relapse for a period of 6 months or more with assessment of time to relapse and treatment of relapsed patients. Both the acute and the relapse prevention trials must be limited to patients capable of giving assent to participate in the trial. 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, from separate longer-term open safety studies, or from controlled studies, e.g., a longer-term safety and efficacy trial. 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, 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.

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

Adolescents (ages 12 to 17 years) 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

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug and its major active metabolite in the above age group. The full spectrum of age strata in the 12-17 year old continuum must be represented (e.g., 12-13, 14-15, 16-17) and must have at least 4 completers per strata. Data from this study must be submitted prior to the start of the safety and efficacy study.

Pediatric Efficacy and Safety Study

- The study must have a sufficient number of patients to provide 80% statistical power to show a difference between drug and placebo. It will probably be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with schizophrenia.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of the study drug at clinically relevant doses identified as effective in an adequately designed trial reflecting the proposed use of the drug. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

Entry Criteria

The protocol must include a valid and reliable diagnostic method for recruiting and enrolling adolescents meeting DSM-IV criteria for schizophrenia. Given the difficulty in making the diagnosis for screening purposes, it is recommended that a clinical interview of children and their parents or caregivers 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 Study

- Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each 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 [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacology (Draft)].

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 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. It may also be useful to add a global measure, e.g., the Clinical Global Impression (CGI). It is essential to identify a primary outcome (or outcomes if more than one is considered important) 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, i.e., vital signs (pulse rate and blood pressure), weight, height, as measured by stadiometer, clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; 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, suicidality and homicidal ideation) as part of this written request. Assessment for the effect of the study drug on the growth and development of pediatric patients is critical, and you must incorporate specific measures to assess changes in height and weight (e.g., stadiometer height measurement).

Statistical Information

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Efficacy and Safety Study

- This trial must have a detailed statistical plan. The trial must be designed with at least 80% statistical power to show a difference between drug and placebo equivalent to the median drug-placebo difference seen in the adult trials that were the basis for this drug's approval, at conventional levels (alpha=0.05, 2-tailed) of statistical significance.

Pediatric Safety Study

- Descriptive analysis of the safety data.

GENERAL REQUIREMENTS AND COMMENTS

Drug Information
Use age appropriate formulations in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

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

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable,

age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug Concerns

No specific concerns related to administration to schizophrenic or manic pediatric patients were identified while studying paliperidone in adults.

Labeling That May Result from the Studies

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

Format of Reports to be Submitted

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

Timeframe for submitting reports of the study(ies)

Reports of the above studies must be submitted to the Agency within 3 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request

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

Please 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. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the

cover letter of the submission.

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

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

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

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

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

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

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population. If you have any questions, contact Keith Kiedrow, Pharm.D., Regulatory Project Manager, at (301) 796-1924.

Sincerely yours,

{See appended electronic signature page}

Robert Temple, M.D.
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/

Robert Temple

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