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/s/

Thomas Laughren
10/11/2006 02:06:25 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
HFD- 860/Biopharm Attention: Raman Baweja	HFD-130/ Division of Psychiatry Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10-06-06		21-520/S-12,20-592/S-39,21-086/S-21,18-936/S-77	New Efficacy Supplements	9-28-06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Symbyax, Zyprexa Zyprexa Zydis, Prozac	Priority Review		**Filing meeting: 11-7-06** **PDUFA date: 3/29/07**

NAME OF FIRM: (b) (4)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Lilly has submitted 4 efficacy supplements for TRD for Symbyax (21-520/S-12), Zyprexa (20-592/S-39), Zyprexa Zydis (21-086/S-21), and Prozac (18-936/S-77). I have included the links of each efficacy supplement in the edr: \\CDSESUB1\N21520\S_012\2006-09-28 \\Cdsesub1\n20592\S_039\2006-09-28 \\CDSESUB1\N18936\S_077\2006-09-28
If you have any questions you can call me at 301-796-1080 or email at renmeet.grewal@fda.hhs.gov .

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Renmeet Grewal, Pharm.D. Regulatory Project Manager 301-796-1080 Renmeet.grewal@fda.hhs.gov	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Renmeet Gujral
10/10/2006 02:42:34 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
HFD- 710/Stat Attention: Peiling Yang	HFD-130/ Division of Psychiatry Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10-10-06		21-520/S-12,20-592/S-39,21-086/S-21,18-936/S-77	New Efficacy Supplements	9-28-06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Symbyax, Zyprexa Zyprexa Zydis, Prozac	Priority Review		**Filing meeting: 11-7-06** **PDUFA date: 3/29/07**

NAME OF FIRM (b) (4)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
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- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
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- ☐ BIOAVAILABILTY STUDIES
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V. SCIENTIFIC INVESTIGATIONS

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COMMENTS/SPECIAL INSTRUCTIONS:

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If you have any questions you can call me at 301-796-1080 or email at renmeet.grewal@fda.hhs.gov .

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Renmeet Grewal, Pharm.D. Regulatory Project Manager 301-796-1080 Renmeet.grewal@fda.hhs.gov	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Renmeet Gujral
10/10/2006 02:44:54 PM

October 17, 2006

This document has been replaced by Acknowledgment Letter dated 10/16/2006.

This document incorrectly states "We will review this application under the provisions of 21 CFR 314 Subpart H (accelerated approval). Before approval of these applications, you must submit copies of all promotional materials, including promotional labeling as well as advertisements, to be used within 120 days after approval."

However this is a supplement and is not approved under subpart H.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your correspondence dated May 21, 2002, requesting changes to FDA's November 30, 2001, Written Request for pediatric studies for Zyprexa (olanzapine).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on November 30, 2001, and amended on April 9, 2002, remain the same.

- **Under ADOLESCENT SCHIZOPHRENIA; General Advice for Developing a Drug for Adolescent- Onset Schizophrenia; Specific Study Requirements for Development Program in Adolescent Schizophrenia; Study Design; Pediatric Efficacy and Safety Study**

  We have amended the clinical design for either inpatient or outpatient status as follows:

  "For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient or outpatient trial, with a recommended duration of at least 6 to 8 weeks."

We note your plans to include patients that meet the diagnostic criteria for schizophrenia, schizophreniform disorder and schizoaffective disorder. Our evaluation will focus on the schizophrenia patients.

- **Under ADOLESCENT BIPOLAR DISORDER; General Advice for Developing a Drug for Mania in Adolescent Bipolar Disorder; Specific Study Requirements for Development Program in Adolescent Mania in Association with Bipolar Disorder; Study Design; Pediatric Efficacy and Safety Study**

  We have amended the clinical design for either inpatient or outpatient status as follows:

  "For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient or outpatient trial, with a recommended duration of at least 3 weeks."

JUL 05 2002

- **Under Format of Reports to be Submitted**

  We have amended the "Format of reports to be submitted" section of your Written Request, which states the specific information on racial and ethnic minorities to be included in the final study report in accordance with Section 18 of the BPCA. Please note that we are changing the word "must" to "should" twice.

  "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(s) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino."

All other terms stated in our original Written Request or any subsequent amendments remain the same.

Reports of the studies that meet the terms of the Written Request dated November 30, 2001, as amended by our letter of April 9, 2002, and by this letter must be submitted to the Agency on or before November 30, 2006, in order to possibly qualify for pediatric exclusivity extension under Section 505A 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. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please 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.

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 (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.

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.

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.

COPY

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

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

COPY

JUL 05 2005

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/s/

Robert Temple
6/29/05 02:20:26 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-592

Lilly Research Laboratories
Attn: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to the Written Request, originally issued on November 30, 2001, that you received from the Center for Drug Evaluation and Research, as well as the amendment issued in July 2002, from the Office of Counter-Terrorism and Pediatric Drug Development.

BPCA § 18: Minority Children and Pediatric Exclusivity Program

We are amending the "Format of reports to be submitted" section of your Written Request to require submitted reports to include more specific information on racial and ethnic minorities, in accordance with Section 18, *Minority Children and Pediatric-Exclusivity Program*, of the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109). All other terms stated in our original Written Request remain the same.

> *Format of reports to be submitted:*
> In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

BPCA § 9: Public Dissemination of Medical and Clinical Pharmacology Review Summaries for All Fileable Supplements Submitted in Response to Written Requests

We note that the July 2002 re-issued Written Request notified you that an application submitted in response to a Written Request would be subject to the disclosure provisions of the BPCA. This letter also reminds you that in accordance with Section 9 of the BPCA, *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 issued or re-issued under BPCA 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.

MAY 1 8 2004

G. Brophy

If you have any questions regarding this letter or the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. If you believe that the Written Request should be amended, please contact the review division directly.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

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/s/

Dianne Murphy
5/7/04 02:05:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-592

Eli Lilly and Company
Attention: H. John Roth, Ph.D.
Sr. Reg. Res. Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Roth:

Please refer to the Written Request, originally issued on November 30, 2001, that you received from the Center for Drug Evaluation and Research. This Written Request was issued under Section 505A of the Federal Food, Drug, and Cosmetic Act to conduct pediatric studies using olanzapine. As you know, on January 4, 2002, the President signed into law the "Best Pharmaceuticals for Children Act," (BPCA) which both extended the pediatric exclusivity program established in the 1997 FDA Modernization Act (FDAMA) and provided new mechanisms for studying pediatric uses for drugs. The BPCA also contains new provisions of which you should be aware related to user fees, priority review, drug labeling, and disclosure of pediatric study results. FDA is revising its Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act to provide additional information on the pediatric drugs study provisions of the BPCA.

FDA has received questions about whether sponsors who were issued Written Requests to conduct pediatric studies prior to passage of the BPCA, but who had not as yet submitted the reports of the studies as of January 4, 2002, would be governed by the provisions of FDAMA or the BPCA. In order to maximize the benefit to be derived from the BPCA and to minimize uncertainty and delay in implementing the pediatric exclusivity program, FDA has decided to reissue those Written Requests originally issued prior to passage of the BPCA for which studies have not already been submitted.

This letter is your notification that the Written Request (and any subsequent amendments) described above is considered to be reissued as of the date of this letter. The terms of the Written Request are not otherwise altered by this letter. If you believe that the Written Request should be amended, please contact the division directly.

Please note that if the original Written Request was issued under Section 505A(a), it will now be considered to be issued under Section 505A(b), due to the reordering of the sections, as described in Section 19 of the BPCA. If the original Written Request was issued under Section 505A(c), it will still be considered to be issued under Section 505A(c).

An important change to note is that, if the drug for which FDA issued the Written Request under 505A(c) has listed patent or exclusivity protection, new section 505(d)(4)(A) states that within 180 days of receipt of this "reissued" Written Request, you must notify FDA when the pediatric studies will be initiated, or that you do not agree to conduct the requested studies. New provisions at Section 505(d)(4)(B)-(F) describe alternative methods for obtaining these pediatric studies.

If you have questions regarding the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. As noted above, requests to amend your Written Request should be directed to the review division.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counterterrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

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/s/

Dianne Murphy
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RECEIVED JUL 17 2002

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592

Eli Lilly and Company
Attention: H. John Roth, Ph.D.
Sr. Reg. Res. Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Roth:

Please refer to your correspondence dated January 28, 2002, requesting changes to FDA's November 30, 2002, Written Request for pediatric studies for Zyprexa (olanzapine).

We reviewed your proposed changes and are amending the following section of the Written Request:

- **Under GENERAL REQUIREMENTS AND COMMENTS; Timeframe for Submitting Reports of the Study(ies)**

  We have amended the timeframe for submitting the reports of the studies from 3 years to 5 years (i.e., on or before November 30, 2006) as follows:

  "Reports of the above studies must be submitted to the Agency within 5 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request."

Your requests to 1) omit the requirement to conduct a relapse prevention trial in adolescent schizophrenia, 2) revise the adolescent bipolar mania study to allow for a flexible dose design, and 3) allow the use of behavioral and/or dietary interventions for patients who gain weight during the trials will be dealt with in a separate letter. All other terms stated in our Written Request remain the same.

Reports of the studies that meet the terms of the Written Request dated November 30, 2002, as amended by this letter must be submitted to the Agency on or before November 30, 2006, in order to possibly qualify for pediatric exclusivity extension under Section 505A 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. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please 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.

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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 (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.

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.

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, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

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

ZY 8264 693

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/s/

Robert Temple
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592

Lilly Research Laboratories
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Reference is made to your Proposed Pediatric Study Request submitted on June 11, 1999, to your New Drug Application for Zyprexa (olanzapine) tablets (NDA 20-592).

We have completed our review of your submission and conclude that your proposed pediatric study request is incomplete.

To obtain needed pediatric information on olanzapine, 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 (1) schizophrenia, and with (2) acute mania, as part of bipolar I disorder, 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 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.

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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 13-17 years.

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.

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.

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Specific Study Requirements for Development Program in Adolescent Schizophrenia

Types of Studies

Pediatric Efficacy and Safety Study

Pediatric Pharmacokinetic 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 Efficacy and Safety Study

- For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient 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. We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug. A relapse prevention trial should follow the acute treatment trial, in which responders 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 should be limited to patients capable of giving assent to participate in the trial.

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 the controlled efficacy trial or to other safety trials. Adequate pharmacokinetic data from studies in a single indication would be sufficient to meet this requirement. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Safety Study

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- 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

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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.

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

Adolescents (ages 13 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 Efficacy and Safety Study

- The study must have a sufficient number of patients to provide reasonable statistical power to show a difference between drug and placebo. While it is difficult to specify the sample size needed to accomplish this, it should be noted that positive trials in adult schizophrenia have generally utilized samples of at least 60 patients per treatment arm. It will probably be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with schizophrenia.

Pediatric Pharmacokinetic Study

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug in the above age group.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of the study drug at clinically relevant doses for a sufficient duration. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

Entry Criteria

The protocols must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with 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 Efficacy and Safety Study

- A scale specific to schizophrenia and sensitive to the effects of drug treatment of schizophrenia in the target population should be used. 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.

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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 should provide estimates of important pharmacokinetic parameters, e.g., AUC, half-life, C_{max}, t_{max}, and apparent oral clearance in pediatric subjects 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/Pharmacological (Draft)].

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, clinical laboratory measures (chemistry, hematology, and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate efficacy in schizophrenia.

Statistical Information

Pediatric Efficacy and Safety Study

- This trial must have a detailed statistical plan. The trial should be designed with at least 80% statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults) at conventional levels (alpha=0.05, 2-tailed) of statistical significance.

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

ADOLESCENT BIPOLAR DISORDER

General Advice for Developing a Drug for Mania in Adolescent 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 13 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the adolescent population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in adolescents should be feasible and should yield useful information.

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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. We believe that a sufficiently strong case has been made for continuity between adult and adolescent bipolar disorder to permit a pediatric claim for a drug already approved in adults for mania to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent mania in association with bipolar disorder. In addition, a pediatric mania program would need to include pharmacokinetic information and safety information in the relevant pediatric age group. For pediatric mania, we consider the relevant age group to include adolescents aged 13-17 years.

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 Development Program in Adolescent Mania in Association with Bipolar Disorder

Types of Studies

Pediatric Efficacy and Safety Study

Pediatric Pharmacokinetic 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 mania in association with bipolar disorder, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Efficacy and Safety Study

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- For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient trial, 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 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. We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug. Given the lack of a robust evidence base for the use of lithium in adolescent mania, there is uncertainty about the optimal therapeutic approach in this population. Thus, this could be a monotherapy trial, or an add-on trial, e.g., adding study drug or placebo to patients already taking lithium. In addition, you may consider a relapse prevention trial to follow from the acute treatment trial, in which responders to acute

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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 should be limited to patients capable of giving assent to participate in the trial.

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 the controlled efficacy trial or to other safety trials. Adequate pharmacokinetic data from studies in a single indication would be sufficient to meet this requirement. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Safety Study

- Safety data must be collected in the controlled efficacy trial. You may consider collecting longer-term safety data. The longer-term safety data could come from open studies, e.g., a longer-term open extension from the controlled efficacy trial and/or in 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.

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

Adolescents (ages 13 to 17 years) must be included in the sample, and there must be a reasonable gender and age distribution.

Number of Patients to be Studied

Pediatric Efficacy and Safety Study

- The study must have a sufficient number of patients to provide reasonable statistical power to show a difference between drug and placebo. While it is difficult to specify the sample size needed to accomplish this, it should be noted that positive trials in adult mania have generally utilized samples of at least 60 patients per treatment arm. It will probably be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with mania.

Pediatric Pharmacokinetic Study

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug in the above age group.

Pediatric Safety Study

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- A sufficient number of pediatric patients in the above age group to adequately characterize the safety of the study drug at clinically relevant doses for a sufficient duration. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

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Entry Criteria

The protocols must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with mania. 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 Efficacy and Safety Study

- A scale specific to mania and sensitive to the effects of drug treatment of mania in the target population should be used. 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 trials, and ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trials.

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 should provide estimates of important pharmacokinetic parameters, e.g., AUC, half-life, C_{max}, t_{max}, and apparent oral clearance in pediatric subjects 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/Pharmacological (Draft)].

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, clinical laboratory measures (chemistry, hematology, and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and you may consider longer-term studies of a year or more to address this question, if the acute studies and any longer-term efficacy studies that you may conduct demonstrate efficacy in bipolar disorder.

Statistical Information

Pediatric Efficacy and Safety Study

- This trial must have a detailed statistical plan. The trial should be designed with at least 80% statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults) at conventional levels (alpha=0.05, 2-tailed) of statistical significance.

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Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

GENERAL REQUIREMENTS AND COMMENTS

Drug Information

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of adolescents (ages 13 to 17), your marketed solid dosage formulation should be adequate for these studies.

Drug Concerns

No specific concerns related to administration to schizophrenic or manic pediatric patients were identified while studying olanzapine in adults, nor have specific concerns been identified during the postmarketing experience.

Labeling That May Result from the Studies

The pediatric schizophrenia and mania efficacy, safety, and pharmacokinetic studies described in this request could result in the addition to labeling of information pertinent to these studies.

Format of Reports to be Submitted

Full study reports or analyses, not previously submitted to the Agency, addressing the issues outlined in this request, with full analysis, assessment, and interpretation.

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 remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

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.

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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**
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.

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.

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 Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

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