DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-192 **NDA APPROVAL**

Vanda Pharmaceuticals
Attention: John Feeney, M.D.
Acting Chief Medical Officer
9605 Medical Center Drive
Suite 300
Rockville, MD 20850

Dear Dr. Feeney:

Please refer to your new drug application (NDA) dated and received September 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fanapt (iloperidone) 1, 2, 4, 6, 8, 10, and 12 mg tablets.

We acknowledge receipt of your submissions and communications dated November 6, 2008, November 19, 2008, January 9, 2009, March 10, 2009, March 17, 2009, April 15, 2009, and April 24, 2009.

Your submission of November 6, 2008 constituted a complete response to our July 25, 2008 action letter.

This new drug application provides for the use of Fanapt (iloperidone) for the acute treatment of schizophrenia in adults.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission **"SPL for approved NDA 22-192."**

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-192**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Fanapt, for this product.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 12 years because necessary studies are highly impractical due to the very low incidence of schizophrenia diagnosed prior to age 13.

We are deferring submission of your pediatric studies for ages 13 to 17 years for this application because the drug is ready for approval in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17. A study to obtain pharmacokinetic data and provide information pertinent to dosing of iloperidone tablets in the relevant pediatric population.

Final Protocol Submission:	by March 1, 2010
Study Completion Date:	by September 1, 2013
Final Report Submission:	by March 1, 2014

2. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17. A study of the efficacy and safety of iloperidone tablets in the relevant pediatric population.

Final Protocol Submission:	by March 1, 2010
Study Completion Date:	by September 1, 2013
Final Report Submission:	by March 1, 2014

Submit final reports to this NDA. Use the following designator to prominently label all submissions:

Required Pediatric Assessment(s)

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of carcinogenicity and to identify an unexpected serious risk of drug interactions.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3. Complete the ongoing P95 carcinogenicity study.

The timetable you submitted on April 24, 2009 states that you will conduct this study according to the following timetable:

Study Completion Date:	by February 28, 2010
Final Report Submission:	by May 31, 2010

4. Conduct a study investigating the possible in vitro interaction of iloperidone and P-Glycoprotein (P-Gp).

The timetable you submitted on April 15, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by August 1, 2009
Study Completion Date:	by October 1, 2009
Final Report Submission:	by November 1, 2009

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of Fanapt (iloperidone) to patients with hepatic dysfunction.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following clinical trial:

5. A repeat of your clinical trial CIL0522A0103, conducted with a group of subjects with mildly and moderately impaired hepatic function, comparing them to normals in the same trial.

The timetable you submitted on April 15, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	by November 1, 2009
Trial Completion Date:	by November 1, 2010
Final Report Submission:	by May 1, 2011

Submit clinical protocols to your IND for this product, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

REQUIRED POSTMARKETING PROTOCOL under 505(o)
REQUIRED POSTMARKETING FINAL REPORT under 505(o)
REQUIRED POSTMARKETING CORRESPONDENCE under 505(o)

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trial required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of the following postmarketing commitment agreed upon in our communication dated April 15, 2009:

6. Long-Term Efficacy Trial

You have agreed to conduct and submit the results of a randomized withdrawal clinical trial to address longer-term efficacy for your drug at appropriate doses.

Protocol Submission:	by November 1, 2009
Trial Completion Date:	by November 1, 2012
Final Report Submission:	by May 1, 2013

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

ADVISORY COMMITTEE

Your application was not referred to an advisory committee for review because this drug is not the first in its class, the clinical study design was acceptable, evaluation of the safety data did not reveal particular safety issues that were unexpected for this class and the efficacy trials did not pose particular concerns.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

DISSOLUTION METHOD AND SPECIFICATIONS

The dissolution method and specification for all strengths of the immediate release tablets should be:

Parameter	Dissolution Method and Specification
Apparatus Type	2 (rotating paddle)
Media	0.1 N HCl
Volume	500 ml
Frequency	50 rpm
Acceptance Criteria	(b) (4)% in 30 minutes

EXPIRY

A 36 month expiry date is granted based on the available stability data.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301) 796-2201.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

5/6/2009 04:36:30 PM