

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 206890

Name: Iloperidone (Tablets), 1mg, 2 mg, 4 mg, 6 mg, 8 mg,
10 mg, and 12 mg

Sponsor: Lupin Pharmaceuticals Inc

Approval Date: May 05, 2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA206890

CONTENTS

Reviews / Information Included in this Review
--

Approval Letter	X
Tentative Approval Letter	
Labeling	X
Labeling Review(s)	
Proprietary Name Review(s)	
Medical Review(s)	
Chemistry Review(s)	
Bio Pharm/Tox Review	
Bioequivalence Review(s)	X
Statistical Review(s)	
Microbiology Review(s)	
Other Review(s)	
Administrative & Correspondence Documents	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206890

APPROVAL LETTER



ANDA 206890

ANDA APPROVAL

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
111 South Calvert Street, Harborplace Tower, 21st Floor
Baltimore, MD 21202
Attention: Debashis Mohanty
Senior Manager, Regulatory Affairs

Dear Debashis Mohanty:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 8, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for loperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg.

Reference is also made to the complete response letter issued by this office on August 25, 2021, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your loperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Fanapt Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg, of Vanda Pharmaceuticals Inc. (Vanda).

The RLD upon which you have based your ANDA, Vanda's Fanapt Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
8,586,610 (the '610 patent)	November 2, 2027
8,652,776 (the '776 patent)	August 31, 2030
8,999,638 (the '638 patent)	October 28, 2030

9,072,742 (the '742 patent)	January 16, 2031
9,074,254 (the '254 patent)	December 28, 2031
9,074,255 (the '255 patent)	December 17, 2030
9,074,256 (the '256 patent)	February 10, 2031
9,138,432 (the '432 patent)	September 30, 2025
9,157,121 (the '121 patent)	April 5, 2030

Your ANDA contains paragraph IV certifications to each of the patents¹ under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of loperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg, under this ANDA. You have notified the Agency that Lupin Limited (Lupin) complied with the requirements of section 505(j)(2)(B) of the FD&C Act.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. 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 (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <https://www.fda.gov/media/128163/download>).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <https://www.fda.gov/media/73013/download>. Information and Instructions for completing the form can be found at <https://www.fda.gov/media/132152/download>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd>.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions² with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling

[21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <https://www.fda.gov/media/71211/download>. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug’s labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled “Changes to an Approved NDA or ANDA” at <https://www.fda.gov/media/71846/download>.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

¹ The Agency notes that the '610, '776, '638, '742, '254, '255, '256, '432, and '121 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

² Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



John
Ibrahim

Digitally signed by John Ibrahim

Date: 5/05/2022 01:02:43PM

GUID: 542af06d0124375c12e8c1d9fc86e87c

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206890

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Iloperidone Tablets safely and effectively. See full prescribing information for Iloperidone Tablets.

Iloperidone tablets Initial U.S. Approval: 2009

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Iloperidone tablets are not approved for use in patients with dementia-related psychosis. (5.1)

RECENT MAJOR CHANGES

Dosage and Administration (2.2)

04/2014

INDICATIONS AND USAGE

Iloperidone Tablets are atypical antipsychotic agent indicated for the treatment of schizophrenia in adults. (1) Efficacy was established in two short-term (4- and 6-week) placebo-and active-controlled studies of adult patients with schizophrenia. (14) In choosing among treatments, prescribers should consider the ability of iloperidone to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate iloperidone slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration.

DOSAGE AND ADMINISTRATION

The recommended target dosage of iloperidone tablets are 12 to 24 mg/day administered twice daily. This target dosage range is achieved by daily dosage adjustments, alerting patients to symptoms of orthostatic hypotension, starting at a dose of 1 mg twice daily, then moving to 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg twice daily on Days 2, 3, 4, 5, 6, and 7 respectively, to reach the 12 mg/day to 24 mg/day dose range. Iloperidone tablets can be administered without regard to meals. (2.1)

DOSAGE FORMS AND STRENGTHS

1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets. (3)

CONTRAINDICATIONS

Known hypersensitivity to iloperidone or to any components in the formulation. (4)

WARNINGS AND PRECAUTIONS

- *Elderly patients with dementia-related psychosis* who are treated with atypical antipsychotic drugs are at an increased risk of death and cerebrovascular-related adverse events, including stroke. (5.1)
- *QT prolongation* Prolongs QT interval and may be associated with arrhythmia and sudden death—consider using other antipsychotics first. Avoid use of iloperidone in combination with other drugs that are known to prolong QTc; use caution and consider dose modification when prescribing iloperidone with other drugs that inhibit iloperidone metabolism. Monitor serum potassium and magnesium in patients at risk for electrolyte disturbances. (1, 5.2, 7.1, 7.3, 12.3)
- *Neuroleptic Malignant Syndrome* Manage with immediate discontinuation of drug and close monitoring. (5.3)
- *Tardive dyskinesia* Discontinue if clinically appropriate. (5.4)

- *Metabolic Changes* Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/ cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.5)
 - o *Hyperglycemia and diabetes mellitus* Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients at risk for diabetes. (5.5)
 - o *Dyslipidemia* Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.5)
 - o *Weight Gain* Weight gain has been reported. Monitor weight. (5.5)
- *Seizures* Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold. (5.6)
- *Orthostatic hypotension* Dizziness, tachycardia, and syncope can occur with standing. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis* have been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue iloperidone at the first sign of a decline in WBC in the absence of other causative factors. (5.8)
- *Suicide* Close supervision of high risk patients. (5.12)
- *Priapism* Cases have been reported in association with iloperidone treatment. (5.13)
- *Potential for cognitive and motor impairment*: Use caution when operating machinery. (5.14)
- See Full Prescribing Information for additional WARNINGS and PRECAUTIONS.

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence $\geq 5\%$ and 2-fold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- The dose of iloperidone should be reduced in patients co-administered a strong CYP2D6 or CYP3A4 inhibitor. (2.2, 7.1)

USE IN SPECIFIC POPULATIONS

- *Pregnancy*: No human or animal data. Use only if clearly needed. (8.1)
- *Nursing Mothers*: Should not breast feed. (8.3)
- *Pediatric Use*: Safety and effectiveness not established in children and adolescents. (8.4)
- *Hepatic Impairment*: Iloperidone tablets are not recommended for patients with severe hepatic impairment. (2.2, 8.7)
- The dose of iloperidone should be reduced in patients who are poor metabolizers of CYP2D6. (2.2, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2014

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Usual Dose
- 2.2 Dosage in Special Populations
- 2.3 Maintenance Treatment
- 2.4 Reinitiation of Treatment in Patients Previously Discontinued
- 2.5 Switching from Other Antipsychotics

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Increased Risks in Elderly Patients with Dementia-Related Psychosis
- 5.2 QT Prolongation
- 5.3 Neuroleptic Malignant Syndrome (NMS)
- 5.4 Tardive Dyskinesia

5.5 Metabolic Changes

5.6 Seizures

5.7 Orthostatic Hypotension and Syncope

5.8 Leukopenia, Neutropenia and Agranulocytosis

5.9 Hyperprolactinemia

5.10 Body Temperature Regulation

5.11 Dysphagia

5.12 Suicide

5.13 Priapism

5.14 Potential for Cognitive and Motor Impairment

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect iloperidone

7.2 Potential for iloperidone to Affect Other Drugs

7.3 Drugs that Prolong the QT Interval

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Smoking Status

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse

10 OVERDOSAGE

- 10.1 Human Experience
- 10.2 Management of Overdose

11 DESCRIPTION**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

- 17.1 QT Interval Prolongation
- 17.2 Neuroleptic Malignant Syndrome
- 17.3 Metabolic Changes
- 17.4 Orthostatic Hypotension
- 17.5 Interference with Cognitive and Motor Performance
- 17.6 Pregnancy
- 17.7 Nursing
- 17.8 Concomitant Medication
- 17.9 Alcohol
- 17.10 Heat Exposure and Dehydration

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo-controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Iloperidone Tablets are not approved for the treatment of patients with Dementia-Related Psychosis. [See **WARNINGS AND PRECAUTIONS (5.1)**]

1 INDICATIONS AND USAGE

Iloperidone tablets are indicated for the treatment of adults with schizophrenia. Efficacy was established in two short-term (4- and 6-week) placebo- and active-controlled studies of adult patients with schizophrenia [See **CLINICAL STUDIES (14)**].

When deciding among the alternative treatments available for this condition, the prescriber should consider the finding that iloperidone is associated with prolongation of the QTc interval [See **WARNINGS AND PRECAUTIONS (5.2)**]. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia which can result in sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether iloperidone will cause torsade de pointes or increase the rate of sudden death is not yet known.

Patients must be titrated to an effective dose of iloperidone. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require a similar titration. Prescribers should be mindful of this delay when selecting an antipsychotic drug for the treatment of schizophrenia [See **DOSAGE AND ADMINISTRATION (2.1)** and **CLINICAL STUDIES (14)**].

The effectiveness of iloperidone in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use iloperidone tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [See **DOSAGE AND ADMINISTRATION (2.3)**].

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dose

Iloperidone tablets must be titrated slowly from a low starting dose to avoid orthostatic hypotension due to its alpha-adrenergic blocking properties. The recommended starting dose for iloperidone tablets is 1 mg twice daily. Dose increases to reach the target range of 6-12 mg twice

daily (12-24 mg/day) may be made with daily dosage adjustments not to exceed 2 mg twice daily (4 mg/day). The maximum recommended dose is 12 mg twice daily (24 mg/day). Iloperidone doses above 24 mg/day have not been systematically evaluated in the clinical trials. Efficacy was demonstrated with iloperidone in a dose range of 6 to 12 mg twice daily. Prescribers should be mindful of the fact that patients need to be titrated to an effective dose of iloperidone. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require similar titration. Prescribers should also be aware that some adverse effects associated with iloperidone use are dose related.

Iloperidone tablets can be administered without regard to meals.

2.2 Dosage in Special Populations

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal impairment status [See **USE IN SPECIFIC POPULATIONS (8.6, 8.7)**].

Dosage adjustment for patients taking iloperidone tablets concomitantly with potential CYP2D6 inhibitors

Iloperidone dose should be reduced by one-half when administered concomitantly with strong CYP2D6 inhibitors such as fluoxetine or paroxetine. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose should then be increased to where it was before [See **DRUG INTERACTIONS (7.1)**].

Dosage adjustment for patients taking iloperidone tablets concomitantly with potential CYP3A4 inhibitors

Iloperidone dose should be reduced by one-half when administered concomitantly with strong CYP3A4 inhibitors such as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is withdrawn from the combination therapy, iloperidone dose should be increased to where it was before [See **DRUG INTERACTIONS (7.1)**].

Dosage adjustment for patients taking iloperidone tablets who are poor metabolizers of CYP2D6: Iloperidone dose should be reduced by one-half for poor metabolizers of CYP2D6 [See **CLINICAL PHARMACOLOGY (12.3)**].

Hepatic Impairment

No dose adjustment to iloperidone is needed in patients with mild hepatic impairment. Exercise caution when administering it to patients with moderate hepatic impairment. Iloperidone is not recommended for patients with severe hepatic impairment [See **USE IN SPECIFIC POPULATIONS (8.7)**].

2.3 Maintenance Treatment

Although there is no body of evidence available to answer the question of how long the patient treated with iloperidone should be maintained, it is generally recommended that responding patients be continued beyond the acute response. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.4 Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that the initiation titration schedule be followed whenever patients have had an interval off iloperidone of more than 3 days.

2.5 Switching from Other Antipsychotics

There are no specific data to address how patients with schizophrenia can be switched from other antipsychotics to iloperidone or how iloperidone can be used concomitantly with other antipsychotics. Although immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

3 DOSAGE FORMS AND STRENGTHS

Iloperidone tablets are available in the following strengths: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg.

1 mg: White, round bevelled edged flat face tablet debossed with “I1” on one side and “L” on the other side.

2 mg: White, round bevelled edged flat face tablet debossed with “I2” on one side and “L” on the other side.

4 mg: White, round bevelled edged flat face tablet debossed with “I4” on one side and “L” on the other side.

6 mg: White, round bevelled edged flat face tablet debossed with “I6” on one side and “L” on the other side.

8 mg: White, round bevelled edged flat face tablet debossed with “I8” on one side and “L” on the other side.

10 mg: White, round bevelled edged flat face tablet debossed with “I10” on one side and “L” on the other side.

12 mg: White, round bevelled edged flat face tablet debossed with “I12” on one side and “L” on the other side.

4 CONTRAINDICATIONS

Iloperidone is contraindicated in individuals with a known hypersensitivity reaction to the product. Reactions have included pruritus and urticaria.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risks in Elderly Patients with Dementia-Related Psychosis

Increased Mortality

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Iloperidone is not approved for the treatment of patients with dementia-related psychosis [See BOXED WARNING].

Cerebrovascular Adverse Events, Including Stroke

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated

patients. Iloperidone are not approved for the treatment of patients with dementia-related psychosis [See **BOXED WARNING**].

5.2 QT Prolongation

In an open-label QTc study in patients with schizophrenia or schizoaffective disorder (n=160), Iloperidone was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of iloperidone on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, iloperidone 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec.

No cases of torsade de pointes or other severe cardiac arrhythmias were observed during the pre-marketing clinical program.

The use of iloperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). Iloperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval; (5) recent acute myocardial infarction; and/or (6) uncompensated heart failure.

Caution is warranted when prescribing iloperidone with drugs that inhibit iloperidone metabolism [See **DRUG INTERACTIONS (7.1)**], and in patients with reduced activity of CYP2D6 [See **CLINICAL PHARMACOLOGY (12.3)**].

It is recommended that patients being considered for iloperidone treatment who are at risk for significant electrolyte disturbances have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Iloperidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Iloperidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

If patients taking iloperidone experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including iloperidone. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of this syndrome should include: (1) immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, which may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely on prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic administered increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, iloperidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful

treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on iloperidone, drug discontinuation should be considered. However, some patients may require treatment with iloperidone despite the presence of the syndrome.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain [See **PATIENT COUNSELING INFORMATION (17.3)**]. While all atypical antipsychotic drugs have been shown to produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including iloperidone. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because iloperidone was not marketed at the time these studies were performed, it is not known if iloperidone is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Data from a 4- week, fixed-dose study in adult subjects with schizophrenia, in which fasting blood samples were drawn, are presented in Table 1.

Table 1. Change in Fasting Glucose

	Placebo	Iloperidone
		24 mg/day
	Mean Change from Baseline(mg/dL)	
	n=114	n=228
Serum Glucose Change from Baseline	-0.5	6.6
	Proportion of Patients with Shifts	
Serum Glucose Normal to High	2.5 %	10.7 %
(<100 mg/dL to ≥126 mg/dL)	(2/80)	(18/169)

Pooled analyses of glucose data from clinical studies including longer term trials are shown in Table 2.

Table 2: Change in Glucose

Mean Change from Baseline (mg/dL)			
	3-6 months	6-12 months	>12 months
Iloperidone 10-16 mg/day	1.8 (N=773)	5.4 (N=723)	5.4 (N=425)
Iloperidone 20-24 mg/day	-3.6 (N=34)	-9.0 (N=31)	-18.0 (N=20)

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Data from a placebo-controlled, 4-week, fixed-dose study, in which fasting blood samples were drawn, in adult subjects with schizophrenia are presented in Table 3.

Table 3. Change in Fasting Lipids

	Placebo	Iloperidone
		24 mg/day
	Mean Change from Baseline (mg/dL)	
	n=114	n=228
Cholesterol		
Change from baseline	-2.17	8.18
LDL	n=109	n=217
Change from baseline	-1.41	9.03
HDL	n=114	n=228
Change from baseline	-3.35	0.55
Triglycerides	n=114	n=228
Change from baseline	16.47	-0.83
	Proportion of Patients with Shifts	
Cholesterol		
Normal to High	1.4%	3.6%
(<200 mg/dL to ≥240 mg/dL)	(1/72)	(5/141)
LDL		
Normal to High	2.4%	1.1%
(<100 mg/dL to ≥160 mg/dL)	(1/42)	(1/90)
HDL		

Normal to Low	23.8%	12.1%
(≥ 40 mg/dL to < 40 mg/dL)	(19/80)	(20/166)
Triglycerides		
Normal to High	8.3%	10.1%
(< 150 mg/dL to ≥ 200 mg/dL)	(6/72)	(15/148)

Pooled analyses of cholesterol and triglyceride data from clinical studies including longer term trials are shown in Tables 4 and 5.

Table 4: Change in Cholesterol

Mean Change from Baseline (mg/dL)			
	3-6 months	6-12 months	>12 months
Iloperidone 10-16 mg/day	-3.9 (N=783)	-3.9 (N=726)	-7.7 (N=428)
Iloperidone 20-24 mg/day	-19.4 (N=34)	-23.2 (N=31)	-19.4 (N=20)

Table 5: Change in Triglycerides

Mean Change from Baseline (mg/dL)			
	3-6 months	6-12 months	>12 months
Iloperidone 10-16 mg/day	-8.9 (N=783)	-8.9 (N=726)	-17.7 (N=428)
Iloperidone 20-24 mg/day	-26.6 (N=34)	-35.4 (N=31)	-17.7 (N=20)

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Across all short- and long-term studies, the overall mean change from baseline at endpoint was 2.1 kg.

Changes in body weight (kg) and the proportion of subjects with $\geq 7\%$ gain in body weight from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in adult subjects are presented in Table 6.

Table 6. Change in Body Weight

		Iloperidone	Iloperidone
	Placebo	10-16 mg/day	20-24 mg/day
	n=576	n=481	n=391
Weight (kg)			
Change from Baseline	-0.1	2.0	2.7
Weight Gain			
$\geq 7\%$ increase from Baseline	4%	12%	18%

5.6 Seizures

In short-term placebo-controlled trials (4- to 6-weeks), seizures occurred in 0.1% (1/1344) of patients treated with iloperidone compared to 0.3% (2/587) on placebo. As with other antipsychotics, iloperidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.7 Orthostatic Hypotension and Syncope

Iloperidone can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. This reflects its alphasadrenergic antagonist properties. In double-blind placebo-controlled short-term studies, where the dose was increased slowly, as recommended above, syncope was reported in 0.4% (5/1344) of patients treated with iloperidone, compared with 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 5% of patients given 20-24 mg/day, 3% of patients given 10-16 mg/day, and 1% of patients given placebo. More rapid titration would be expected to increase the rate of orthostatic hypotension and syncope.

Iloperidone should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.8 Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue iloperidone at the first sign of a decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $<1000/\text{mm}^3$) should discontinue iloperidone and have their WBC followed until recovery.

5.9 Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, iloperidone elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadalsteroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Mammary gland proliferative changes and increases in serum prolactin were seen in mice and rats treated with iloperidone [See **NONCLINICAL TOXICOLOGY (13.1)**]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In a short-term placebo-controlled trial (4-weeks), the mean change from baseline to endpoint in plasma prolactin levels for the iloperidone 24 mg/day-treated group was an increase of 2.6 ng/mL compared to a decrease of 6.3 ng/mL in the placebo-group. In this trial, elevated plasma prolactin levels were observed in 26% of adults treated with iloperidone compared to 12% in the placebo group. In the short-term trials, iloperidone was associated with modest levels of prolactin elevation compared to greater prolactin elevations observed with some other antipsychotic agents. In pooled analysis from clinical studies including longer term trials, in 3210 adults treated with iloperidone, gynecomastia was reported in 2 male subjects (0.1%) compared to 0% in placebo-treated patients, and galactorrhea was reported in 8 female subjects (0.2%) compared to 3 female subjects (0.5%) in placebo-treated patients.

5.10 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing iloperidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.11 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Iloperidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia [See **BOXED WARNING**].

5.12 Suicide

The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for iloperidone should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

5.13 Priapism

Three cases of priapism were reported in the pre-marketing iloperidone program. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Iloperidone shares this pharmacologic activity. Severe priapism may require surgical intervention.

5.14 Potential for Cognitive and Motor Impairment

iloperidone, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported in 11.9% (104/874) of adult patients treated with iloperidone at doses of 10 mg/day or greater versus 5.3% (31/587) treated with placebo. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with iloperidone does not affect them adversely.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of

another drug and may not reflect the rates observed in clinical practice. The information below is derived from a clinical trial database for iloperidone consisting of 2070 patients exposed to iloperidone at doses of 10 mg/day or greater, for the treatment of schizophrenia. Of these, 806 received iloperidone for at least 6 months, with 463 exposed to iloperidone for at least 12 months. All of these patients who received iloperidone were participating in multiple-dose clinical trials. The conditions and duration of treatment with iloperidone varied greatly and included (in overlapping categories), open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and short-term and longer-term exposure.

Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions, reactions were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportions of individuals who experienced a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The information presented in these sections was derived from pooled data from -4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in patients who received iloperidone at daily doses within a range of 10 to 24 mg (n=874).

Adverse Reactions Occurring at an Incidence of 2% or More among Iloperidone -Treated Patients and More Frequent than Placebo

Table 7 enumerates the pooled incidences of treatment-emergent adverse reactions that were spontaneously reported in four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, listing those reactions that occurred in 2% or more of patients treated with iloperidone in any of the dose groups, and for which the incidence in iloperidone -treated patients in any dose group was greater than the incidence in patients treated with placebo.

Table 7:Percentage of Treatment-Emergent Adverse Reactions in Short-Term, Fixed- or Flexible-Dose, Placebo-Controlled Trials in Adult Patients*

Body System or Organ Class	Percentage of Patients Reporting Reaction		
	Placebo %	Iloperidone 10-16 mg/day %	Iloperidone 20-24 mg/day %
Dictionary-derived Term	(N=587)	(N=483)	(N=391)
Body as a Whole			
Arthralgia	2	3	3
Fatigue	3	4	6
Musculoskeletal Stiffness	1	1	3
Weight Increased	1	1	9
Cardiac Disorders			
Tachycardia	1	3	12
Eye Disorders			
Vision Blurred	2	3	1
Gastrointestinal Disorders			
Nausea	8	7	10
Dry Mouth	1	8	10
Diarrhea	4	5	7
Abdominal Discomfort	1	1	3
Infections			
Nasopharyngitis	3	4	3
Upper Respiratory Tract Infection	1	2	3
Nervous System Disorders			
Dizziness	7	10	20
Somnolence	5	9	15
Extrapyramidal Disorder	4	5	4
Tremor	2	3	3
Lethargy	1	3	1
Reproductive System			
Ejaculation Failure	<1	2	2
Respiratory			
Nasal Congestion	2	5	8
Dyspnea	<1	2	2
Skin			
Rash	2	3	2
Vascular Disorders			
Orthostatic Hypotension	1	3	5
Hypotension	<1	<1	3

*Table includes adverse reactions that were reported in 2% or more of patients in any of the iloperidone dose groups and which occurred at greater incidence than in the placebo group. Figures rounded to the nearest integer.

Dose-Related Adverse Reactions in Clinical Trials

Based on the pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, adverse reactions that occurred with a greater than 2% incidence in the patients treated

with iloperidone, and for which the incidence in patients treated with iloperidone 20-24 mg/day were twice than the incidence in patients treated with iloperidone 10-16 mg/day were: abdominal discomfort, dizziness, hypotension, musculoskeletal stiffness, tachycardia, and weight increased.

Common and Drug-Related Adverse Reactions in Clinical Trials

Based on the pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, the following adverse reactions occurred in $\geq 5\%$ incidence in the patients treated with iloperidone and at least twice the placebo rate for at least 1 dose: dizziness, dry mouth, fatigue, nasal congestion, somnolence, tachycardia, orthostatic hypotension, and weight increased. Dizziness, tachycardia, and weight increased were at least twice as common on 20-24 mg/day as on 10-16 mg/day.

Extrapyramidal Symptoms (EPS) in Clinical Trials

Pooled data from the 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies provided information regarding treatment-emergent EPS. Adverse event data collected from those trials showed the following rates of EPS-related adverse events as shown in Table 8.

Table 8: Percentage of EPS Compared to Placebo

	Placebo (%) (N=587)	Iloperidone 10-16 mg/day (%) (N=483)	Iloperidone 20-24 mg/day (%) (N=391)
Adverse Event Term			
All EPS events	11.6	13.5	15.1
Akathisia	2.7	1.7	2.3
Bradykinesia	0	0.6	0.5
Dyskinesia	1.5	1.7	1.0
Dystonia	0.7	1.0	0.8
Parkinsonism	0	0.2	0.3
Tremor	1.9	2.5	3.1

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

Based on the pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, there was no difference in the incidence of discontinuation due to adverse events between iloperidone -treated (5%) and placebo-treated (5%) patients. The types of adverse events that led to discontinuation were similar for the iloperidone - and placebo-treated patients.

Demographic Differences in Adverse Reactions in Clinical Trials

An examination of population subgroups in the 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies did not reveal any evidence of differences in safety on the basis of age, gender or race [See **WARNINGS AND PRECAUTIONS (5.1)**].

Laboratory Test Abnormalities in Clinical Trials

There were no differences between iloperidone and placebo in the incidence of discontinuation due to changes in hematology, urinalysis, or serum chemistry.

In short-term placebo-controlled trials (4- to 6-weeks), there were 1.0% (13/1342) iloperidone-treated patients with hematocrit at least one time below the extended normal range during post-randomization treatment, compared to 0.3% (2/585) on placebo. The extended normal range for lowered hematocrit was defined in each of these trials as the value 15% below the normal range for the centralized laboratory that was used in the trial.

Other Reactions During the Pre-marketing Evaluation of iloperidone

The following is a list of MedDRA terms that reflect treatment-emergent adverse reactions in patients treated with iloperidone at multiple doses ≥ 4 mg/day during any phase of a trial with the database of 3210 iloperidone -treated patients. All reported reactions are included except those already listed in Table 7, or other parts of the **ADVERSE REACTIONS (6)** section, those considered in the **WARNINGS AND PRECAUTIONS (5)**, those reaction terms which were so general as to be uninformative, reactions reported in fewer than 3 patients and which were neither serious nor life-threatening, reactions that are otherwise common as background reactions, and reactions considered unlikely to be drug related. It is important to emphasize that, although the reactions reported occurred during treatment with iloperidone, they were not necessarily caused by it.

Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not listed in Table 7 appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic Disorders

Infrequent - anemia, iron deficiency anemia; ***Rare*** - leukopenia

Cardiac Disorders

Frequent - palpitations; ***Rare*** - arrhythmia, atrioventricular block first degree, cardiac failure (including congestive and acute)

Ear and Labyrinth Disorders

Infrequent - vertigo, tinnitus

Endocrine Disorders

Infrequent - hypothyroidism

Eye Disorders

Frequent - conjunctivitis (including allergic); ***Infrequent*** - dry eye, blepharitis, eyelid edema, eye swelling, lenticular opacities, cataract, hyperemia (including conjunctival)

Gastrointestinal Disorders

Infrequent -gastritis, salivary hypersecretion, fecal incontinence, mouth ulceration; ***Rare*** - aphthous stomatitis, duodenal ulcer, hiatus hernia, hyperchlorhydria, lip ulceration, reflux esophagitis, stomatitis

General Disorders and Administrative Site Conditions

Infrequent - edema (general, pitting, due to cardiac disease), difficulty in walking, thirst; ***Rare*** - hyperthermia

Hepatobiliary Disorders: Infrequent - cholelithiasis

Investigations: Frequent: weight decreased; ***Infrequent*** - hemoglobin decreased, neutrophil count increased, hematocrit decreased

Metabolism and Nutrition Disorders: Infrequent - increased appetite, dehydration, hypokalemia, fluid retention

Musculoskeletal and Connective Tissue Disorders

Frequent - myalgia, muscle spasms; **Rare** - torticollis

Nervous System Disorders

Infrequent - paresthesia, psychomotor hyperactivity, restlessness, amnesia, nystagmus;

Rare - restless legs syndrome

Psychiatric Disorders

Frequent - restlessness, aggression, delusion; **Infrequent** - hostility, libido decreased, paranoia, anorgasmia, confusional state, mania, catatonia, mood swings, panic attack, obsessive-compulsive disorder, bulimia nervosa, delirium, polydipsia psychogenic, impulse-control disorder, major depression

Renal and Urinary Disorders

Frequent - urinary incontinence; **Infrequent** - dysuria, pollakiuria, enuresis, nephrolithiasis;

Rare - urinary retention, renal failure acute

Reproductive System and Breast Disorders

Frequent - erectile dysfunction; **Infrequent** - testicular pain, amenorrhea, breast pain; **Rare** - menstruation irregular, gynecomastia, menorrhagia, metrorrhagia, postmenopausal hemorrhage, prostatitis.

Respiratory, Thoracic and Mediastinal Disorders

Infrequent - epistaxis, asthma, rhinorrhea, sinus congestion, nasal dryness; **Rare** - dry throat, sleep apnea syndrome, dyspnea exertional

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of iloperidone: retrograde ejaculation. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

Given the primary CNS effects of iloperidone, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. Due to its - alpha 1-adrenergic receptor antagonism, iloperidone has the potential to enhance the effect of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect iloperidone

Iloperidone is not a substrate for CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. This suggests that an interaction of iloperidone with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for iloperidone metabolism. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., fluoxetine, paroxetine) can inhibit iloperidone elimination and cause increased blood levels.

Ketoconazole

Co-administration of ketoconazole (200 mg twice daily for 4 days), a potent inhibitor of CYP3A4, with a 3 mg single dose of iloperidone to 19 healthy volunteers, ages 18-45 years,

increased the area under the curve (AUC) of iloperidone and its metabolites P88 and P95 by 57%, 55% and 35%, respectively. Iloperidone doses should be reduced by about one-half when administered with ketoconazole or other strong inhibitors of CYP3A4 (e.g., itraconazole). Weaker inhibitors (e.g., erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level.

Fluoxetine

Coadministration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29-44 years, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2- to 3- fold, and decreased the AUC of its metabolite P95 by one-half. Iloperidone doses should be reduced by one-half when administered with fluoxetine. When fluoxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to the previous level.

Paroxetine

Coadministration of paroxetine (20 mg/day for 5-8 days), a potent inhibitor of CYP2D6, with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 years resulted in increased mean steady-state peak concentrations of iloperidone and its metabolite P88, by about 1.6 fold, and decreased mean steady-state peak concentrations of its metabolite P95 by one-half. Iloperidone doses should be reduced by one-half when administered with paroxetine. When paroxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to previous levels.

Paroxetine and Ketoconazole

Coadministration of paroxetine (20 mg once daily for 10 days), a CYP2D6 inhibitor, and ketoconazole (200 mg twice daily) with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 years resulted in a 1.4 fold increase in steady-state concentrations of iloperidone and its metabolite P88 and a 1.4 fold decrease in the P95 in the presence of paroxetine. So giving iloperidone with inhibitors of both of its metabolic pathways did not add to the effect of either inhibitor given alone. Iloperidone doses should therefore be reduced by about one-half if administered concomitantly with both a CYP2D6 and CYP3A4 inhibitor.

7.2 Potential for iloperidone to Affect Other Drugs

In vitro studies in human liver microsomes showed that iloperidone does not substantially inhibit the metabolism of drugs metabolized by the following cytochrome P450 isozymes: CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, or CYP2E1. Furthermore, *in vitro* studies in human liver microsomes showed that iloperidone does not have enzyme inducing properties, specifically for the following cytochrome P450 isozymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5.

Dextromethorphan

A study in healthy volunteers showed that changes in the pharmacokinetics of dextromethorphan (80 mg dose) when a 3 mg dose of iloperidone was co-administered resulted in a 17% increase in total exposure and a 26% increase in the maximum plasma concentrations ($C_{\max}$) of dextromethorphan. Thus, an interaction between iloperidone and other CYP2D6 substrates is unlikely.

Fluoxetine

A single 3 mg dose of iloperidone had no effect on the pharmacokinetics of fluoxetine (20 mg twice daily).

Midazolam (a sensitive CYP 3A4 substrate)

A study in patients with schizophrenia showed a less than 50% increase in midazolam total exposure at iloperidone steady state (14 days of oral dosing at up to 10 mg iloperidone twice daily) and no effect on midazolam $C_{\max}$. Thus, an interaction between iloperidone and other CYP3A4 substrates is unlikely.

7.3 Drugs that Prolong the QT Interval

Iloperidone should not be used with any other drugs that prolong the QT interval [See **WARNINGS AND PRECAUTIONS (5.2)**].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Iloperidone caused developmental toxicity, but was not teratogenic, in rats and rabbits.

In an embryo-fetal development study, pregnant rats were given 4, 16, or 64 mg/kg/day (1.6, 6.5, and 26 times the maximum recommended human dose (MRHD) of 24 mg/day on a mg/m^2 basis) of iloperidone orally during the period of organogenesis. The highest dose caused increased early intrauterine deaths, decreased fetal weight and length, decreased fetal skeletal ossification, and an increased incidence of minor fetal skeletal anomalies and variations; this dose also caused decreased maternal food consumption and weight gain.

In an embryo-fetal development study, pregnant rabbits were given 4, 10, or 25 mg/kg/day (3, 8, and 20 times the MRHD on a mg/m^2 basis) of iloperidone during the period of organogenesis. The highest dose caused increased early intrauterine deaths and decreased fetal viability at term; this dose also caused maternal toxicity.

In additional studies in which rats were given iloperidone at doses similar to the above beginning from either pre-conception or from day 17 of gestation and continuing through weaning, adverse reproductive effects included prolonged pregnancy and parturition, increased stillbirth rates, increased incidence of fetal visceral variations, decreased fetal and pup weights, and decreased post-partum pup survival. There were no drug effects on the neurobehavioral or reproductive development of the surviving pups. No-effect doses ranged from 4 to 12 mg/kg except for the increase in stillbirth rates which occurred at the lowest dose tested of 4 mg/kg, which is 1.6 times the MRHD on a mg/m^2 basis. Maternal toxicity was seen at the higher doses in these studies.

The iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present in significant amounts in rats, was given to pregnant rats during the period of organogenesis at oral doses of 20, 80, or 200 mg/kg/day. No teratogenic effects were

seen. Delayed skeletal ossification occurred at all doses. No significant maternal toxicity was produced. Plasma levels of P95 (AUC) at the highest dose tested were 2 times those in humans receiving the MRHD of iloperidone.

There are no adequate and well-controlled studies in pregnant women.

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Iloperidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of iloperidone on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Iloperidone was excreted in milk of rats during lactation. It is not known whether iloperidone or its metabolites are excreted in human milk. It is recommended that women receiving iloperidone should not breast feed.

8.4 Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

8.5 Geriatric Use

Clinical Studies of iloperidone in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 years and over to determine whether or not they respond differently than younger adult patients. Of the 3210 patients treated with iloperidone in premarketing trials, 25 (0.5%) were ≥ 65 years old and there were no patients ≥ 75 years old.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile (i.e., increased risk in mortality and cerebrovascular events including stroke) in this population compared to younger patients with schizophrenia [See **BOXED WARNING** and **WARNINGS AND PRECAUTIONS (5.1)**]. The safety and efficacy of iloperidone in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with iloperidone, vigilance should be exercised.

8.6 Renal Impairment

Because iloperidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a significant impact on the pharmacokinetics of iloperidone. Renal impairment (creatinine clearance < 30 mL/min) had minimal effect on $C_{\max}$ of iloperidone (given in a single dose of 3 mg) and its metabolites P88 and P95 in any of the 3

analytes measured. AUC_{0-∞} was increased by 24%, decreased by 6%, and increased by 52% for iloperidone, P88 and P95, respectively, in subjects with renal impairment.

8.7 Hepatic Impairment

No dose adjustment to FANAPT is needed in patients with mild hepatic impairment. Exercise caution when administering it to patients with moderate hepatic impairment. Iloperidone is not recommended for patients with severe hepatic impairment [See **DOSAGE IN SPECIAL POPULATIONS (2.2)**].

In adult subjects with mild hepatic impairment no relevant difference in pharmacokinetics of iloperidone, P88 or P95 (total or unbound) was observed compared to healthy adult controls. In subjects with moderate hepatic impairment a higher (2-fold) and more variable free exposure to the active metabolites P88 was observed compared to healthy controls, whereas exposure to iloperidone and P95 was generally similar (less than 50% change compared to control). Since a study in severe liver impaired subjects has not been conducted, iloperidone is not recommended for patients with severe hepatic impairment.

8.8 Smoking Status

Based on *in vitro* studies utilizing human liver enzymes, iloperidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of iloperidone.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Iloperidone is not a controlled substance.

9.2 Abuse

Iloperidone has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this experience the extent to which a CNS active drug, iloperidone, will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of iloperidone misuse or abuse (e.g. development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

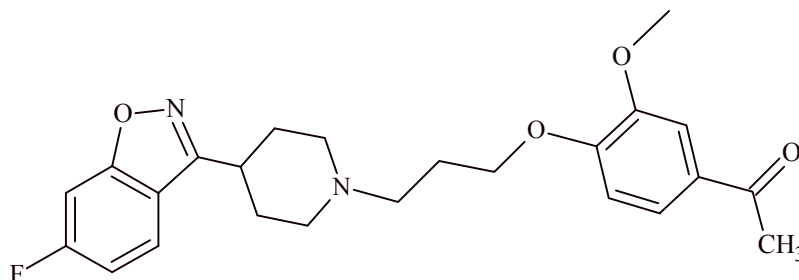
In pre-marketing trials involving over 3210 patients, accidental or intentional overdose of iloperidone was documented in 8 patients ranging from 48 mg to 576 mg taken at once and 292 mg taken over a -3-day period. No fatalities were reported from these cases. The largest confirmed single ingestion of iloperidone was 576 mg; no adverse physical effects were noted for this patient. The next largest confirmed ingestion of iloperidone was 438 mg over a -4-day period; extrapyramidal symptoms and a QTc interval of 507 msec were reported for this patient with no cardiac sequelae. This patient resumed iloperidone treatment for an additional 11 months. In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects (e.g., drowsiness and sedation, tachycardia and hypotension) of iloperidone.

10.2 Management of Overdose

There is no specific antidote for iloperidone. Therefore appropriate supportive measures should be instituted. In case of acute overdose, the physician should establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of iloperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of iloperidone, resulting in problematic hypotension. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of iloperidone -induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision should continue until the patient recovers.

11 DESCRIPTION

Iloperidone is a psychotropic agent belonging to the chemical class of piperidinyl-benzisoxazole derivatives. Its chemical name is 4'-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]propoxy]-3'-methoxyacetophenone. Its molecular formula is $C_{24}H_{27}FN_2O_4$ and its molecular weight is 426.48. The structural formula is:



Iloperidone is a white to off-white beige solid powder. It is practically insoluble in water, very slightly soluble in 0.1 N HCl and freely soluble in chloroform, ethanol, methanol, and acetonitrile.

Iloperidone tablets are intended for oral administration only. Each round, uncoated tablet contains 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg of iloperidone. Inactive ingredients are: colloidal silicon dioxide, hypromellose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, sodium starch glycolate. The tablets are white, round, flat, bevelled edged and identified with logos "I1", "I2", "I4", "I6", "I8", "I10" and "I12" debossed on one side and "L" (for all strength) on other side.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of iloperidone, as with other drugs having efficacy in schizophrenia, is unknown. However it is proposed that the efficacy of iloperidone is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonisms.

12.2 Pharmacodynamics

Iloperidone exhibits high (nM) affinity binding to serotonin 5-HT_{2A}, dopamine D₂ and D₃ receptors, and norepinephrine NE α ₁ receptors (K_i values of 5.6, 6.3, 7.1, and 0.36 nM, respectively). Iloperidone has moderate affinity for dopamine D₄, and serotonin 5-HT₆ and 5-HT₇ receptors (K_i values of 25, 43, and 22, nM respectively), and low affinity for the serotonin 5-HT_{1A}, dopamine D₁, and histamine H₁ receptors (K_i values of 168, 216 and 437 nM, respectively). Iloperidone has no appreciable affinity (K_i > 1000 nM) for cholinergic muscarinic receptors. Iloperidone functions as an antagonist at the dopamine D₂, D₃, serotonin 5-HT_{1A} and norepinephrine α ₁/ α _{2C} receptors. The affinity of the iloperidone metabolite P88 is generally equal or less than that of the parent compound. In contrast, the metabolite P95 only shows affinity for 5-HT_{2A} (K_i value of 3.91) and the NE α _{1A}, NE α _{1B}, NE α _{1D}, and NE α _{2C} receptors (K_i values of 4.7, 2.7, 8.8 and 4.7 nM respectively).

12.3 Pharmacokinetics

The observed mean elimination half-lives for iloperidone, P88 and P95 in CYP2D6 extensive metabolizers (EM) are 18, 26, and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37 and 31 hours, respectively. Steady-state concentrations are attained within 3-4 days of dosing. Iloperidone accumulation is predictable from single-dose pharmacokinetics. The pharmacokinetics of iloperidone is more than dose proportional. Elimination of iloperidone is mainly through hepatic metabolism involving 2 P450 isozymes, CYP2D6 and CYP3A4.

Absorption

Iloperidone is well absorbed after administration of the tablet with peak plasma concentrations occurring within 2 to 4 hours; while the relative bioavailability of the tablet formulation compared to oral solution is 96%. Administration of iloperidone with a standard high-fat meal did not significantly affect the C_{max} or AUC of iloperidone, P88, or P95, but delayed T_{max} by 1 hour for iloperidone, 2 hours for P88 and 6 hours for P95. Iloperidone can be administered without regard to meals.

Distribution

Iloperidone has an apparent clearance (clearance / bioavailability) of 47 to 102 L/h, with an apparent volume of distribution of 1340-2800 L. At therapeutic concentrations, the unbound fraction of iloperidone in plasma is ~ 3% and of each metabolite (P88 and P95) it is ~8%.

Metabolism and Elimination

Iloperidone is metabolized primarily by 3 biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and O-demethylation (mediated by CYP3A4). There are 2 predominant iloperidone metabolites, P95 and P88. The iloperidone metabolite P95 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively.

Approximately 7% - 10% of Caucasians and 3% - 8% of black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas

the rest are intermediate, extensive or ultrarapid metabolizers. Coadministration of iloperidone with known strong inhibitors of CYP2D6 like fluoxetine results in a 2.3 fold increase in iloperidone plasma exposure, and therefore one-half of the iloperidone dose should be administered.

Similarly, PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs.

The bulk of the radioactive materials were recovered in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with feces accounting for 19.9% (EM) to 22.1% (PM) of the dosed radioactivity.

Transporter Interaction

Iloperidone and P88 are not substrates of P-gp and iloperidone is a weak P-gp inhibitor.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in CD-1 mice and Sprague Dawley rats. Iloperidone was administered orally at doses of 2.5, 5.0 and 10 mg/kg/day to CD-1 mice and 4, 8, and 16 mg/kg/day to Sprague Dawley rats (0.5, 1.0 and 2.0 times and 1.6, 3.2 and 6.5 times, respectively, the --MRHD- of 24 mg/day on a mg/m² basis). There was an increased incidence of malignant mammary gland tumors in female mice treated with the lowest dose (2.5 mg/kg/day) only. There were no treatment-related increases in neoplasia in rats.

The carcinogenic potential of the iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present at significant amounts in mice or rats, was assessed in a lifetime carcinogenicity study in Wistar rats at oral doses of 25, 75 and 200 mg/kg/day in males and 50, 150, and 250 (reduced from 400) mg/kg/day in females.

Drug-related neoplastic changes occurred in males, in the pituitary gland (pars distalis adenoma) at all doses and in the pancreas (islet cell adenoma) at the high dose. Plasma levels of P95 (AUC) in males at the tested doses (25, 75, and 200 mg/kg/day) were approximately 0.4, 3, and 23 times, respectively, the human exposure to P95 at the MRHD of iloperidone.

An increase in mammary, pituitary and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D2 antagonism and hyperprolactinemia. Increases in serum prolactin were seen in mice and rats treated with iloperidone. The relevance of these tumor findings in rodents in terms of human risk is unknown.

Mutagenesis

Iloperidone was negative in the Ames test and in the *in vivo* mouse bone marrow and rat liver micronucleus tests. Iloperidone induced chromosomal aberrations in Chinese Hamster Ovary (CHO) cells *in vitro* at concentrations which also caused some cytotoxicity.

The iloperidone metabolite P95 was negative in the Ames test, the V79 chromosome aberration test, and an *in vivo* mouse bone marrow micronucleus test.

Impairment of Fertility

Iloperidone decreased fertility at 12 and 36 mg/kg in a study in which both male and female rats were treated. The no-effect dose was 4 mg/kg, which is 1.6 times the -MHRD of 24 mg/day on a mg/m² basis.

14 CLINICAL STUDIES

The efficacy of iloperidone in the treatment of schizophrenia was supported by 2 placebo- and active-controlled short-term (4- and 6-week) trials. Both trials enrolled patients who met the DSM-III/IV criteria for schizophrenia.

Two instruments were used for assessing psychiatric signs and symptoms in these studies. The Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia.

A 6-week, placebo-controlled trial (n=706) involved 2 flexible dose ranges of iloperidone (12-16 mg/day or 20-24 mg/day) compared to placebo and an active control (risperidone). For the 12-16 mg/day group, the titration schedule of iloperidone was 1 mg twice daily on Days 1 and 2, 2 mg twice daily on Days 3 and 4, 4 mg twice daily on Days 5 and 6, and 6 mg twice daily on Day 7. For the 20-24 mg/day group, the titration schedule of iloperidone was 1 mg twice daily on Day 1, 2 mg twice daily on Day 2, 4 mg twice daily on Day 3, 6 mg twice daily on Days 4 and 5, 8 mg twice daily on Day 6, and 10 mg twice daily on Day 7. The primary endpoint was change from baseline on the BPRS total score at the end of treatment (Day 42). Both the 12-16 mg/day and the 20-24 mg/day dose ranges of iloperidone were superior to placebo on the BPRS total score. The active control antipsychotic drug appeared to be superior to iloperidone in this trial within the first 2 weeks, a finding that may in part be explained by the more rapid titration that was possible for that drug. In patients in this study who remained on treatment for at least 2 weeks, iloperidone appeared to have had comparable efficacy to the active control.

A 4-week, placebo-controlled trial (n=604) involved one fixed dose of iloperidone (24 mg/day) compared to placebo and an active control (ziprasidone). The titration schedule for this study was similar to that for the 6-week study. This study involved titration of iloperidone starting at 1 mg twice daily on Day 1 and increasing to 2, 4, 6, 8, 10 and 12 mg twice daily on Days 2, 3, 4, 5, 6, and 7. The primary endpoint was change from baseline on the PANSS total score at the end of treatment (Day 28). The 24 mg/day iloperidone dose was superior to placebo in the PANSS total score. Iloperidone appeared to have similar efficacy to the active control drug which also needed a slow titration to the target dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

Iloperidone Tablets are supplied in the following strengths and package configurations:

Tablet Strength	Description	Package Configuration	NDC Code
1 mg	White, round bevelled edged flat face tablet debossed with “11” on one side and “L” on the other side.	Bottles of 60	68180-812-07
2 mg	White, round bevelled edged flat face tablet debossed with “12” on one side and “L” on the other side.	Bottles of 60	68180-813-07
4 mg	White, round bevelled edged flat face tablet debossed with “14” on one side and “L” on the other side.	Bottles of 60	68180-814-07
6 mg	White, round bevelled edged flat face tablet debossed with “16” on one side and “L” on the other side.	Bottles of 60	68180-815-07
8 mg	White, round bevelled edged flat face tablet debossed with “18” on one side and “L” on the other side.	Bottles of 60	68180-816-07
10 mg	White, round bevelled edged flat face tablet debossed with “I10” on one side and “L” on the other side.	Bottles of 60	68180-817-07
12 mg	White, round bevelled edged flat face tablet debossed with “I12” on one side and “L” on the other side.	Bottles of 60	68180-818-07

Storage

Store Iloperidone tablets at controlled room temperature, 25°C (77°F); excursions permitted to 15 to 30 °C (59 to 86°F) [See USP Controlled Room Temperature]. Protect Iloperidone tablets from exposure to light and moisture.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe iloperidone tablets:

17.1 QT Interval Prolongation

Patients should be advised to consult their physician immediately if they feel faint, lose consciousness or have heart palpitations. Patients should be counseled not to take iloperidone with other drugs that cause QT interval prolongation [See **WARNINGS AND PRECAUTIONS (5.2)**]. Patients should be told to inform physicians that they are taking iloperidone before any new drug is taken.

17.2 Neuroleptic Malignant Syndrome

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including iloperidone. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) [See **WARNINGS AND PRECAUTIONS (5.3)**].

17.3 Metabolic Changes

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those who develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment. Patients should be counseled that weight gain has occurred during treatment with iloperidone. Clinical monitoring of weight is recommended. [See **WARNINGS AND PRECAUTIONS (5.5)**].

17.4 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose [See **WARNINGS AND PRECAUTIONS (5.7)**].

17.5 Interference with Cognitive and Motor Performance

Because iloperidone may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that iloperidone therapy does not affect them adversely [See **WARNINGS AND PRECAUTIONS (5.14)**].

17.6 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with iloperidone [See **USE IN SPECIFIC POPULATIONS (8.1)**].

17.7 Nursing

Patients should be advised not to breastfeed an infant if they are taking iloperidone [See **USE IN SPECIFIC POPULATIONS (8.3)**].

17.8 Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions [See **DRUG INTERACTIONS (7)**].

17.9 Alcohol

Patients should be advised to avoid alcohol while taking iloperidone.

17.10 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

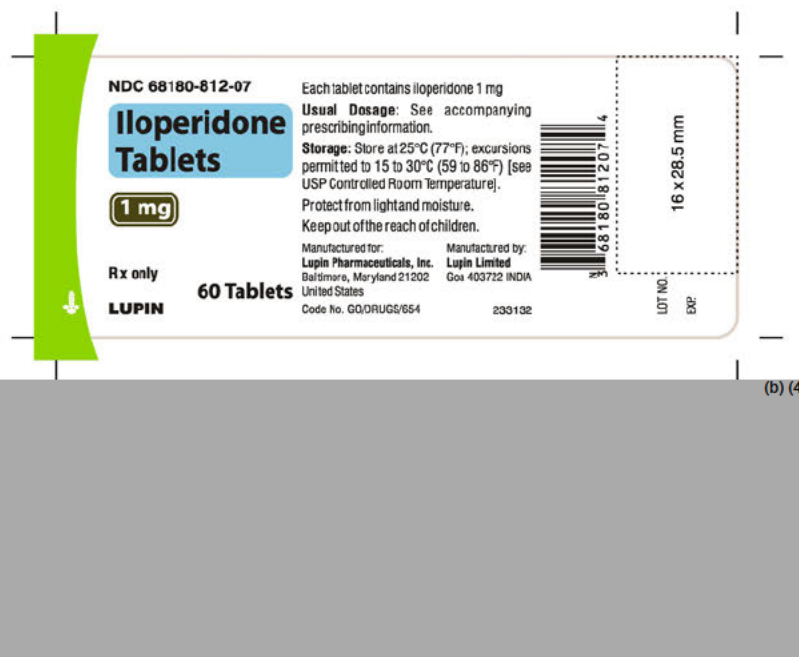
Lupin Limited

Goa 403 722

INDIA

May 2014

Artwork for USFDA Submission 2014



The image shows the artwork for a box of Iloperidone Tablets. The box is white with a green vertical band on the left side. The text on the box includes the NDC number, product name, dosage, and manufacturer information. A large grey rectangular area at the bottom of the page is redacted.

NDC 68180-812-07

Iloperidone Tablets

1 mg

Rx only

LUPIN

60 Tablets

Each tablet contains iloperidone 1 mg

Usual Dosage: See accompanying prescribing information.

Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Protect from light and moisture.
Keep out of the reach of children.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States

Manufactured by:
Lupin Limited
Gos 403722 INDIA

Code No. GQ/DRUGS/664

233192

LOT NO.
EXP

16 x 28.5 mm

(b) (4)

Artwork for USFDA Submission 2014

NDC 68180-813-07

Iloperidone Tablets

2 mg

Rx only

LUPIN

60 Tablets

Each tablet contains iloperidone 2 mg

Usual Dosage: See accompanying prescribing information.

Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Protect from light and moisture.
Keep out of the reach of children.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States

Manufactured by:
Lupin Limited
Gos 403722 INDIA

Code No. GQ/DRUGS/664

239193

LOT NO.
EXP

16 x 28.5 mm

68180-81307-1

(b) (4)

Artwork for USFDA Submission 2014

NDC 68180-814-07

**Iloperidone
Tablets**

4 mg

Rx only

LUPIN

60 Tablets

Each tablet contains iloperidone 4 mg

Usual Dosage: See accompanying prescribing information.

Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Protect from light and moisture.

Keep out of the reach of children.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States

Code No. GQ/DRUGS/664

Manufactured by:
Lupin Limited
Goa 403722 INDIA

233194



16 x 28.5 mm

LOT NO.
EXP

(b) (4)

Artwork for USFDA Submission 2014

NDC 68180-815-07 Each tablet contains iloperidone 6 mg

Iloperidone Tablets **Usual Dosage:** See accompanying prescribing information.

6 mg **Storage:** Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Rx only **60 Tablets** Protect from light and moisture. Keep out of the reach of children.

LUPIN Manufactured for: **Lupin Pharmaceuticals, Inc.** Baltimore, Maryland 21202 United States
Code No. GQ/DRUGS/664

Manufactured by: **Lupin Limited** Goa 403722 INDIA
233195

LOT NO. EXP.

16 x 28.5 mm

(b) (4)

Artwork for USFDA Submission 2014

NDC 68180-816-07

Iloperidone Tablets

8 mg

Rx only

LUPIN

60 Tablets

Each tablet contains iloperidone 8 mg

Usual Dosage: See accompanying prescribing information.

Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Protect from light and moisture.
Keep out of the reach of children.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States

Manufactured by:
Lupin Limited
Gos 403722 INDIA

Code No. GQ/DRUGS/664

233196

LOT NO.
EXP

16 x 28.5 mm

68180-816-07-2

(b) (4)

Artwork for USFDA Submission 2014

NDC 68180-817-07

Iloperidone Tablets

10 mg

Rx only

LUPIN

60 Tablets

Each tablet contains iloperidone 10 mg

Usual Dosage: See accompanying prescribing information.

Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Protect from light and moisture.
Keep out of the reach of children.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States

Manufactured by:
Lupin Limited
Gos 403722 INDIA

Code No. GQ/DRUGS/664

233197

LOT NO.
EXP

16 x 28.5 mm

(b) (4)

Artwork for USFDA Submission 2014

NDC 68180-818-07

Iloperidone Tablets

12 mg

Rx only

LUPIN

60 Tablets

Each tablet contains iloperidone 12 mg

Usual Dosage: See accompanying prescribing information.

Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Protect from light and moisture.
Keep out of the reach of children.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States
Code No. GQ/DRUGS/664

Manufactured by:
Lupin Limited
Gos 403722 INDIA
233198

LOT NO.
EXP

16 x 28.5 mm

68180-818-07 6

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 206890

BIOEQUIVALENCE REVIEW(s)

**DIVISION OF BIOEQUIVALENCE
DISSOLUTION ACKNOWLEDGEMENT REVIEW**

ANDA No.	206890
Drug Product Name	Iloperidone Tablets
Strength (s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12mg
Applicant Name	Lupin Limited
Applicant Address	159, CST Road Kalina, Santacruz (East) Mumbai, India 400098
US Agent Name and the mailing address	Dr. William McIntyre Lupin Pharmaceuticals, Inc. 111 South Calvert Street Harborplace Tower, 21st Floor Baltimore, Maryland 21202
US Agent's Telephone Number	(410) 576-2000
US Agent's Fax Number	(410) 576-2221
Original Submission Date(s)	05/08/2014
Submission Date(s) of Amendment(s) Under Review	03/18/2015
First Generic	No
Reviewer	Tiffany Pokora, Pharm.D.
OVERALL DISSOLUTION REVIEW RESULT	ADEQUATE

EXECUTIVE SUMMARY

This is a review of the dissolution method and/or specification acknowledgement from the firm. The firm has accepted the following FDA-recommended dissolution method and specification(s).

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm
Temperature:	37°C ± 0.5°C
Media:	0.1 N Hydrochloric Acid
Volume:	500 mL
Specification:	NLT ^(b) ₍₄₎ % (Q) dissolved in 30 minutes

RESPONSE FROM FIRM:

The Division of Bioequivalence (DB) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) studies and the waiver requests will be conducted later.

Your dissolution testing using the FDA-recommended method is acceptable. However, your proposed specification, NLT (b) (4)% (Q) in (b) (4) minutes, is not acceptable. Please acknowledge the following FDA-recommended dissolution method and specification:

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm
Temperature:	37°C ± 0.5°C
Media:	0.1 N Hydrochloric Acid
Volume:	500 mL
Specification:	NLT (b) (4)% (Q) dissolved in 30 minutes

As recommended by the agency, we have revised the Dissolution Specification from “NLT (b) (4)% (Q) in (b) (4) Minutes” to “NLT (b) (4)% (Q) in 30 Minutes”. We acknowledge the FDA recommended Dissolution Method and Specification. The brief summary of the same is provided in the Table below for the reference.

USP Apparatus	Type II (Paddle)
Rotational Speed	50 rpm
Temperature	37°C ± 0.5°C
Media	0.1 N Hydrochloric Acid (b) (4)
Volume	500 mL
Specification	NLT (b) (4)% (Q) dissolved in 30 minutes

RECOMMENDATIONS

From a bioequivalence point of view, the firm has met the requirements for in-vitro dissolution testing. The dissolution testing section of the application is adequate and we have no further questions at this time.

APPEARS THIS WAY ON
ORIGINAL

DISSOLUTION COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA:	206890
APPLICANT:	Lupin Limited
DRUG PRODUCT:	Iloperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg

The Division of Bioequivalence II (DBII) has completed its review of your submission acknowledged on the coversheet and has no further questions at this time. We acknowledge that you will conduct the dissolution testing of your test product using the following FDA-recommended dissolution method and specification:

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm
Temperature:	37°C ± 0.5°C
Media:	0.1 N Hydrochloric Acid
Volume:	500 mL
Specification:	NLT (b)(4) % (Q) dissolved in 30 minutes

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
 Director
 Division of Bioequivalence II
 Office of Generic Drugs
 Center for Drug Evaluation and Research

COMPLETED ASSIGNMENT FOR 206890 ID: 25732

Reviewer: Pokora, Tiffany

Date Completed: 04/10/2015

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Dissolution Acknowledgement

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
25732	4/10/2015	Dissolution Data (REGULAR)	Dissolution Acknowledgement	1	0
				Total:	0

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	206890	
Drug Product Name	Iloperidone Tablets	
Strength(s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg & 12 mg	
Applicant Name	Lupin Limited	
Applicant Address	Lupin Limited, 159, CST Road Kalina, Santacruz (East) Mumbai, Maharashtra 400098 INDIA	
US Agent Name and the mailing address	Mr. Debashis Mohanty (Senior Regulatory Affairs Associate) Lupin Pharmaceuticals, Inc., 111 South Calvert Street Harborplace Tower, 21st Floor Baltimore, Maryland 21202	
US agent's Telephone Number	(410) 5762000	
US Agent's Fax Number	(410) 5762221	
Original Submission Date(s)	05/08/2014	
Submission Date(s) of Amendment(s) Under Review	05/08/2014, 09/30/2014	
Reviewer	Ganlin Zhao	
Study Number (s)	ILOP-1K-569-13/ LBC-13-080	ILOP-1K-570-13/ LBC-13-081
Study Type (s)	Fasting	Fed
Strength (s)	1 mg	1 mg
Clinical Site	Micro Therapeutic Research Labs Private Limited	
Clinical Site Address, Phone #, Fax #	Micro Therapeutic Research Labs Private Limited, No.6, Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059. Tamil Nadu, India. Phone: +91 44 22390070 – 72. Fax : +91-44-22390068	
Analytical Site	Lupin Bioresearch Center	
Analytical Site Address, Phone #, Fax #	Lupin Bioresearch Center, Sai Trinity A Wing, Unit 1, 2, 3 & 4, Survey No. 146/2/1B, Pashan, Pune – 411021, Maharashtra, India Ph.: +91-20-66219200 Fax: +91-20-66219224	
OSIS Status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☒ Complete	<u>Year 3 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection

OVERALL REVIEW RESULT	ADEQUATE		
REVISED/NEW DRAFT GUIDANCE INCLUDED	NO		
COMMUNICATION	☐ ECD ☐ IR ☒ NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 3	FASTING	1 MG	ADEQUATE
1, 3	FED	1 MG	ADEQUATE
1, 3, 5	WAIVER	2 MG	ADEQUATE
1, 3, 5	WAIVER	4 MG	ADEQUATE
1, 3, 5	WAIVER	6 MG	ADEQUATE
1, 3, 5	WAIVER	8 MG	ADEQUATE
1, 3, 5	WAIVER	10 MG	ADEQUATE
1, 3, 5	WAIVER	12 MG	ADEQUATE

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product Iloperidone Tablets, 1 mg, manufactured by Lupin Limited, to the corresponding reference product Fanapt® (Iloperidone) Tablets, 1 mg, (b) (4) distributed by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The firm's fasting and fed BE studies are acceptable. The results are summarized in the tables below.

Reference Scaled Average Bioequivalence Approach Used				No		
Iloperidone Tablets 1mg Dose (3 x 1mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals-Firm Calculated Fasting Bioequivalence Study (Study No. ILOP-1K-569-13/ LBC-13-080)						
Iloperidone						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
Ln(AUC0-t)	50425.3797	28	51239.4368	28	98.41	94.71 to 102.25
Ln(AUC0-∞)	56927.1901	28	57485.7671	28	99.03	95.06 to 103.17
Cmax	3510.8062	28	3504.0978	28	100.19	93.59 to 107.26
(active p88 metabolite)-Firm Calculated						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
Ln(AUC0-t)	87082.4343	28	84788.7799	28	102.71	98.79 to 106.77
Ln(AUC0-∞)	103740.096	28	93753.9542	28	110.65	95.49 to 128.23
Ln(Cmax)	3633.9882	28	3612.0581	28	100.61	95.12 to 106.41

Iloperidone P88-Reviewer Calculated							
PK Parameter	N	Geometric Least Square Mean		T/R Ratio (%)	90% Confidence Interval		Power_80
		T	R		LCI	UCI	
Ln(C _{max})	28	3634.0	3612.1	100.61	95.11	106.42	1.0000
Ln(AUC _{0-t})	28	87402.4	85046.6	102.77	98.86	106.84	1.0000
Ln(AUC _{0-∞})*	28	95962.4	93825.5	102.28	98.49	106.21	1.0000

*The reviewer used different time points from the firm to calculate AUC_{0-∞} for subject 29 in the period of test treatment in the fasting study.

Reference Scaled Average Bioequivalence Approach Used				No		
Iloperidone Tablets 1mg Dose (3 x 1mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals-Firm Calculated Fed Bioequivalence Study (Study No. ILOP-1K-570-13/ LBC-13-081)						
Iloperidone						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
Ln(AUC0-t)	52342.3821	29	51427.5583	29	101.78	97.34 to 106.42
Ln(AUC0-∞)	59678.6629	29	58772.7872	29	101.54	97.74 to 105.49
Ln(Cmax)	2783.0641	29	2863.0469	29	97.21	91.07 to 103.76
(active p88 metabolite)						

Parameter	Test	N	RLD	N	Ratio	90% C.I.
Ln(AUC _{0-t})	85098.4020	29	84907.0535	29	100.23	96.45 to 104.15
Ln(AUC _{0-∞})	94787.1171	29	94972.7130	29	99.80	96.01 to 103.74
Ln(C _{max})	3045.7058	29	3129.2174	29	97.33	92.54 to 102.37

In the fasting and fed BE studies, the pharmacokinetic (PK) parameters of the test and reference products for the active metabolite iloperidone P88 were comparable. Therefore, the metabolite data are supportive.

The firm's test formulations of all 7 strengths are acceptable. The formulations of the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths of the test product are proportionally similar to that of the bio-strength, 1 mg.

The dissolution data for quality control and stability purpose have been previously reviewed¹. According to the dissolution-only review, the firm has conducted acceptable comparative dissolution testing on all 7 strengths of the Iloperidone Tablets using the FDA recommended dissolution method² [500 mL of 0.1 N Hydrochloric Acid, Apparatus II (Paddle) at 50 rpm]. Since (b) (4) % of drug release has been achieved at 15 minute time point for the test product for all 7 strengths (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg), the calculation of f₂ values are not necessary for comparison of the dissolution profiles of the test products. All 7 strengths of the test products are (b) (4) dissolved in the dissolution medium. The dissolution profiles of 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths of the test product are considered comparable. The dissolution data are adequate with respect to supporting waiver request of the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths.

The Division of Bioequivalence I (DBI) grants the waiver requests for in vivo BE study requirements for the following strengths: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg based on criteria set forth in 21 CFR § 320.22 (d) (2).

The 90% CIs of the PK parameters of iloperidone all fall well within the BE criteria of 80.00-125.00%. The evaluation of the submitted data for the in vivo BE studies does not indicate any conduct issues and no data integrity deficiency was identified by the reviewer. The Office of Study Integrity and Surveillance (OSIS) inspection of the study site is NOT expected to impact the BE study outcomes. No OSIS inspection is pending or necessary for the clinical site and analytical site in the current ANDA.

The application is adequate with no deficiencies.

¹ Panorama: ANDA 206890: Biopharmaceutical Quality Review, by Katherine Szeszypalow, 02/25/2015 and Tiffany Pokora, 04/10/2015

<http://panorama.fda.gov/task/view?ID=5421498b005b8e1a00d0e0717a066237>

² http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm

2 TABLE OF CONTENTS

1	Executive Summary	3
2	Table of Contents	5
3	Submission Summary.....	6
3.1	Drug Product Information.....	6
3.2	PK/PD Information	6
3.3	OGD Recommendations for Drug Product	7
3.4	Pre-Study Bioanalytical Method Validation	8
3.5	In Vivo Studies.....	12
3.6	Waiver Request(s) For Immediate Release Dosage Forms	21
3.7	Deficiency Comments.....	21
3.8	Comments for Other OGD Disciplines	21
4	Appendix	22
4.1	Individual Study Reviews	22
4.1.1	Single-dose Fasting Bioequivalence Study.....	22
4.1.1.1	Study Design.....	22
4.1.1.2	Clinical Results.....	25
4.1.1.3	Bioanalytical Results	29
4.1.1.4	Pharmacokinetic Results.....	32
4.1.2	Single-dose Fed Bioequivalence Study	43
4.1.2.1	Study Design.....	43
4.1.2.2	Clinical Results.....	47
4.1.2.3	Bioanalytical Results	51
4.1.2.4	Pharmacokinetic Results.....	54
4.2	Formulation Data	63
4.3	Dissolution Data (Applicable if there are waiver requests).....	68

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Iloperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg & 12 mg
Reference Product	Fanapt® (Iloperidone) Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg & 12 mg*
RLD Manufacturer	(b) (4)
NDA No.	022192
RLD Approval Date	May 6, 2009
Indication	FANAPT is an atypical antipsychotic agent indicated for the treatment of schizophrenia in adults.

*Only Fanapt (iloperidone) Tablets 1 mg is designated as the RLD in the Orange Book.

3.2 PK/PD Information³

Bioavailability	The relative bioavailability of the tablet formulation compared to oral solution is 96%.
Food Effect	Administration of iloperidone with a standard high-fat meal did not significantly affect the C _{max} or AUC of iloperidone, P88, or P95, but delayed T _{max} by 1 hour for iloperidone, 2 hours for P88 and 6 hours for P95. FANAPT can be administered without regard to meals.
T_{max}	2 to 4 hours
Metabolism	Iloperidone is metabolized primarily by three biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and O-demethylation (mediated by CYP3A4). There are two predominant iloperidone metabolites, P95 and P88. The iloperidone metabolite P95 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively. Iloperidone and P88 are not substrates of P-gp and iloperidone is a weak P-gp inhibitor.
Excretion	Elimination of iloperidone is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. The bulk of the radioactive materials were recovered in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with feces accounting for 19.9% (EM) to 22.1% (PM) of the dosed radioactivity.
Half-life	The observed mean elimination half-lives for iloperidone, P88 and P95 in CYP2D6 extensive metabolizers (EM) are 18, 26 and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37 and 31 hours, respectively.

³ Electronic Orange Book, search term: Fanapt, last accessed on April, 2015.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo

Dosage and Administration	The recommended target dosage of FANAPT tablets is 12 to 24 mg/day administered twice daily. This target dosage range is achieved by daily dosage adjustments, alerting patients to symptoms of orthostatic hypotension, starting at a dose of 1 mg twice daily, then moving to 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg twice daily on Days 2, 3, 4, 5, 6, and 7 respectively, to reach the 12 mg/day to 24 mg/day dose range. FANAPT can be administered without regard to meals.
Maximum Daily Dose	24 mg (12 mg twice daily)

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed
---------------------------------------	--------------------

1.	Type of study:	Fasting
	Design:	Single-dose, two-way crossover <i>in-vivo</i>
	Strength:	1 mg (dose=1 mg*2 or 1 mg*3 depending on the assay sensitivity)
	Subjects:	Normal healthy males and nonpregnant females, general population
	Additional Comments:	

2.	Type of study:	Fed
	Design:	Single-dose, two-way crossover <i>in-vivo</i>
	Strength:	1 mg (dose=1 mg*2 or 1 mg*3 depending on the assay sensitivity)
	Subjects:	Normal healthy males and nonpregnant females, general population
	Additional Comments:	The test and reference products should be administered 30 minutes after start of the meal.

Analytes to measure (in plasma/serum/blood):	Iloperidone and the active P88 metabolite in plasma	
Bioequivalence based on:	Iloperidone (90% CI)	
Waiver request of in-vivo testing:	2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg	
Source of most recent recommendations or provide the link to the current draft guidance:	Draft Guidance on Iloperidone (November 2010) at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081325.htm	
Summary of OGD or DB History	Pending ANDAs (Not Yet Reviewed)	Yes (multiple ANDAs per product search in DARRTS)
	Approved ANDAs	No (currently there is no listing of the generic iloperidone tablets in the Orange Book)
	Previously Reviewed ANDAs	Yes (one per product search in DARRTS: ANDA 205480)
	Protocols	No

	Controls	Yes (none of the controls are from the current applicant)
--	----------	---

3.4 Pre-Study Bioanalytical Method Validation

Bioanalytical Method Validation (Fasting Study and Fed Study)	
Parameters	Data
Bioanalytical method validation report location	Appendix 16.5.1 of the Clinical Study Report
Analyte	Iloperidone
Internal standard (IS)	Iloperidone D3
Method description	Solid Phase Extraction
Limit of quantitation	100.510 pg/mL for Iloperidone
Average recovery of drug (%)	HQC: 96.47% MQC: 93.74% LQC: 96.64%
Average recovery of IS (%)	99.22%
Standard curve concentrations (pg/mL)	100.510 to 10052.291
QC concentrations (pg/mL)	Iloperidone HQC: 7141.096 MQC: 4141.836 LQC: 277.503 LLOQQC: 100.512
QC Intraday precision range (%)	Iloperidone HQC: 1.08-2.95% MQC: 0.91-3.97% LQC: 1.03-7.51% LLOQQC: 2.77-11.30%
QC Intraday accuracy range (%)	Iloperidone HQC: 99.54-111.07% MQC: 98.55-107.74% LQC: 97.45-109.77% LLOQQC: 92.19-108.87%
QC Interday precision range (%)	Iloperidone 4.05% to 9.77%
QC Interday accuracy range (%)	Iloperidone 100.79% to 103.80%
Bench-top stability (hrs)	06 hours and 32 minutes at room temperature
Solution stability	Iloperidone Short term stock solution stability: Iloperidone: 08 hours and 10minutes at room temperature Iloperidone D3: 08 hours and 10minutes at room temperature Short term spiking solution stability: Iloperidone: 08 hours and 10minutes at room temperature Iloperidone D3: 08 hours and 10minutes at room temperature Iloperidone Long term stock solution stability: Iloperidone: 56 days at 2-8°C Iloperidone D3: 56 days at 2-8°C Long term spiking solution stability: Iloperidone: 55 days and 22 hours at 2-8°C Iloperidone D3: 55 days and 55 hours at 2-8°C

Processed stability (hrs)	Auto sampler stability: 53 hours and 52 minutes at 10°C Post extract stability: 24 Hours and 36 minutes at 2-8°C and 03 hours 10 minutes at room temperature		
Freeze-thaw stability (cycles)	4 cycles at -30°C and -75°C		
Long-term storage stability (days)	56 days at -30°C and -75°C		
Dilution integrity	Starting from 16284.711pg/mL of Iloperidone in plasma (about 1.62 times the concentration of the highest standard)		
	Dilution factor	Two times	Four times
	%Accuracy	99.97	97.03
	%CV	1.91	1.65
Selectivity	No interfering peaks noted in blank plasma samples		

Parameters	Data
Bioanalytical method validation report location	Appendix 16.5.1 of the Clinical Study Report
Analyte	Iloperidone P88
Internal standard (IS)	Iloperidone P88 D3
Method description	Solid Phase Extraction
Limit of quantitation	100.349 pg/mL for Iloperidone P88
Average recovery of drug (%)	HQC: 90.52% MQC: 86.89% LQC: 87.77%
Average recovery of IS (%)	87.40%
Standard curve concentrations (pg/mL)	100.349 to 10036.159
QC concentrations (pg/mL)	Iloperidone P88 HQC: 7129.646 MQC: 4135.194 LQC: 277.058 LLOQQC: 100.350
QC Intraday precision range (%)	Iloperidone P88 HQC: 2.31-5.02% MQC: 2.65-4.16% LQC: 3.13-7.60% LLOQQC: 5.72-17.34%
QC Intraday accuracy range (%)	Iloperidone P88 HQC: 99.68-103.90% MQC: 97.55-102.20% LQC: 87.63-103.65% LLOQQC: 88.99-98.64%
QC Interday precision range (%)	Iloperidone P88 3.74% to 10.56%
QC Interday accuracy range (%)	Iloperidone P88 94.41% to 101.22%
Bench-top stability (hrs)	06 hours and 32 minutes at room temperature
Solution stability	Iloperidone P88 Short term stock solution stability: Iloperidone P88: 08 hours and 10minutes at room

	temperature Iloperidone P88 D3: 08 hours and 10minutes at room temperature Short term spiking solution stability: Iloperidone P88: 08 hours and 10minutes at room temperature Iloperidone P88 D3: 08 hours and 10minutes at room temperature Iloperidone P88 Long term stock solution stability: Iloperidone: 56 days at 2-8°C Iloperidone D3: 56 days at 2-8°C Long term spiking solution stability: Iloperidone: 55 days and 22 hours at 2-8°C Iloperidone D3: 55 days and 22 hours at 2-8°C		
Processed stability (hrs)	Auto sampler stability: 53 hours and 52 minutes at 10°C Post extract stability: 24 Hours and 36 minutes at 2-8 °C and 03 hours 10 minutes at room temperature		
Freeze-thaw stability (cycles)	4 cycles at -30°C and -75°C		
Long-term storage stability (days)	56 days at -30°C and -75°C		
Dilution integrity	Starting from 16258.578pg/mL of Iloperidone P88 in plasma (about 1.62 times the concentration of the highest standard)		
	Dilution factor	Two times	Four times
	%Accuracy	99.95	101.06
	%CV	2.22	2.10
Selectivity	No interfering peaks noted in blank plasma samples		

SOPs submitted	Yes
Does the duration of the each of the LTSS stability parameters support the sample preparation and assay dates	Yes

Comments on the Pre-Study Method Validation:

1. The LTSS is 56 days at -30°C and -75°C for both Iloperidone and Iloperidone P88. The sample storage time is 36 days at -30°C ± 05°C in the fasting study ILOP-1K-569-13/ LBC-13-080, and 39 days at -30°C ± 05°C in the fed study ILOP-1K-570-13/ LBC-13-081. The study plasma samples were transferred from the clinical site to the analytical site at -75°C ± 10°C. The LTSS data are sufficient to cover the storage period of study samples during fasting and fed studies.

2. According to the method SOP AAP-13-014-00 (Title: Estimation of Iloperidone and Iloperidone P88 in Human Plasma using UPLC-MS/MS; effective date 4/15/2013), the assay simultaneously quantitated iloperdone and iloperidone P88 from human plasma. The standard curve samples and quality control samples were prepared as a mixture of iloperidone and iloperidone P88.
3. The method validation is acceptable.

3.5 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Title	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) – Iloperidone						Study Report Location
					Cmax (pg/mL) (N=28)	Tmax (hr) (N=28)	AUC _{0-t} (pg*hr/mL) (N=28)	AUC _∞ (pg*hr/mL) (N=28)	T½ (hr) (N=28)	Kel (hr-1) (N=28)	
Study # ILOP-1K-569-13/LBC-13-080	An open label, balanced, randomized, single-dose, two treatment, two period, two sequence, two way crossover, oral bioequivalence study of Iloperidone Tablets 1 mg of Lupin limited, India and Fanapt® (Iloperidone) (b) (4)	Randomized single-dose crossover	Test product (T) Iloperidone Tablets 1 mg [Batch # G390074]	28 completing (Male) Healthy subjects mean age 28.68 years (21-39 years)	4012.3215±2339.4344	2.00 (1.00-4.00)	57322.2177 ± 35670.1232	64259.0917 ± 39048.9106	25.786 ± 8.199	0.0300 ± 0.0109	Refer Fasting Study Report body
					(CV %) 58.31		(CV %) 62.23	(CV %) 60.77	(CV %) 31.80	(CV %) 36.18	
					3948.7021±1755.6714	2.00 (1.00-3.50)	56901.1610 ± 28345.3230	63135.0795 ± 30477.2113	24.606 ± 6.922	0.0305 ± 0.0091	
					(CV %) 44.46		(CV %) 49.82	(CV %) 48.27	(CV %) 28.13	(CV %) 29.75	
					Distributed by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936, in healthy, adult, human male subjects, under fasting conditions.						

Study Ref. No.	Study Title	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) – active P88 metabolite						Study Report Location
					Cmax (pg/mL) (N=28)	Tmax (hr) (N=28)	AUC _{0-t} (pg*hr/mL) (N=28)	AUC _∞ (pg*hr/mL) (N=28)	T _{1/2} (hr) (N=28)	Kel (hr-1) (N=28)	
Study # ILOP-1K-569-13/LBC-13-080	An open label, balanced, randomized, single-dose, two treatment, two period, two sequence, two way crossover, oral bioequivalence study of Iloperidone Tablets 1 mg of Lupin limited, India and Fanapt® (Iloperidone) (b) (4)	Randomized single-dose crossover	Test product (T) Iloperidone Tablets 1 mg [Batch # G390074]	28 completing (Male) Healthy subjects mean age 28.68 years (21-39 years)	3919.3668 ± 1589.6558	2.75 (1.50-6.00)	95767.5912 ± 46070.2323	114284.3659 ± 59788.2166	83.400 ± 293.713	0.0251 ± 0.0075	Refer Fasting Study Report body
					(CV %) 40.56		(CV %) 48.11	(CV %) 52.32	(CV %) 352.17	(CV %) 30.03	
					3969.5012 ± 1807.7351	2.00 (1.00-4.00)	93640.5203 ± 43164.9390	104049.3895 ± 50834.6194	29.303 ± 6.751	0.0253 ± 0.0077	
					(CV %) 45.54		(CV %) 46.10	(CV %) 48.86	(CV %) 23.04	(CV %) 30.45	
	Distributed by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936, in healthy, adult, human male subjects, under fasting conditions.		Ref. product (R) Fanapt® (Iloperidone) Tablets 1 mg [Lot # FFZN]								

Study Ref. No.	Study Title	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) – Iloperidone						Study Report Location
					Cmax (pg/mL) (N=29)	Tmax (hr) (N=29)	AUC _{0-t} (pg*hr/mL) (N=29)	AUC _∞ (pg*hr/mL) (N=29)	T½ (hr) (N=29)	Kel (hr-1) (N=29)	
Study # ILOP-1K-570-13/LBC-13-081	An open label, balanced, randomized, single-dose, two treatment, two period, two sequence, two way crossover, oral bioequivalence study of Iloperidone Tablets 1 mg of Lupin limited, India and Fanapt® (Iloperidone) (b) (4)	Randomized single-dose crossover	Test product (T) Iloperidone Tablets 1 mg [Batch # G390074]	29 completin g (Male) Healthy subjects mean age 29.21 years (20-42 years)	3019.9901 ± 1211.6461	3.00 (2.00-10.00)	56156.6772 ± 25654.0394	63760.5992 ± 28526.2591	27.935 ± 9.417	0.0279 ± 0.0101	Refer Fed Study Report body
					(CV %) 40.12		(CV %) 45.68	(CV %) 44.74	(CV %) 33.71	(CV %) 36.18	
					3034.1579 ± 1077.0255		56129.8499 ± 29168.7686	63543.8820 ± 31562.1575	28.097 ± 8.085	0.0269 ± 0.0084	
					(CV %) 35.50		(CV %) 51.97	(CV %) 49.67	(CV %) 28.77	(CV %) 31.14	
	Distributed by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936, in healthy, adult, human male subjects, under fed conditions.		Ref. product (R) Fanapt® (Iloperidone) Tablets 1 mg [Lot # FFZN]								

Study Ref. No.	Study Title	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) – active P88 metabolite						Study Report Location
					C _{max} (pg/mL) (N=29)	T _{max} (hr) (N=29)	AUC _{0-t} (pg*hr/mL) (N=29)	AUC _∞ (pg*hr/mL) (N=29)	T _½ (hr) (N=29)	K _{el} (hr ⁻¹) (N=29)	
Study # ILOP-1K-570-13/LBC-13-081	An open label, balanced, randomized, single-dose, two treatment, two period, two sequence, two way crossover, oral bioequivalence study of Iloperidone Tablets 1 mg of Lupin limited, India and Fanapt® (Iloperidone) Tablets 1 mg (b) (4)	Randomized single-dose crossover	Test product (T) Iloperidone Tablets 1 mg [Batch # G390074]	29 completing (Male) Healthy subjects mean age 29.21 years (20-42 years)	3261.6138 ± 942.5238	5.00 (2.00-10.00)	91403.9117 ± 23089.5739	101153.2150 ± 26565.7709	27.867 ± 6.387	0.0262 ± 0.0061	Refer Fed Study Report body
					(CV %) 28.90		(CV %) 25.26	(CV %) 26.26	(CV %) 22.92	(CV %) 23.21	
					3320.2413 ± 977.6737	5.00 (2.00-8.00)	90074.5516 ± 23800.1688	99768.2276 ± 25776.0060	30.218 ± 7.540	0.0241 ± 0.0049	
					(CV %) 29.45		(CV %) 26.42	(CV %) 25.84	(CV %) 24.95	(CV %) 20.40	
	Distributed by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936, in healthy, adult, human male subjects, under fed conditions.		Ref. product (R) Fanapt® (Iloperidone) Tablets 1 mg [Lot # FFZN]								

Table 2. Reanalysis of Study Samples

Study Code: : LBC-13-080 Fasting Study Analyte: Iloperidone								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.00%	0.00%	0.0	0.0	0.00%	0.00%
D	1.0	0.0	0.10%	0.00%	1.0	0.0	0.10%	0.00%
E	2.0	1.0	0.20%	0.10%	2.0	1.0	0.20%	0.10%
F	6.0	4.0	0.59%	0.39%	1.0	0.0	0.10%	0.00%
G	1.0	0.0	0.10%	0.00%	1.0	0.0	0.10%	0.00%
Total	10.0	5.0	0.98%	0.49%	5.0	1.0	0.49%	0.10%

Code E: IS Variation

Code D: Sample concentration exceeding ULOQ

Code F: Response in predose sample

Code G: Poor Chromatography

Study Code: : LBC-13-080 Fasting Study Analyte: Iloperidone P88								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.00%	0.00%	0.0	0.0	0.00%	0.00%
E	4.0	1.0	0.39%	0.10%	3.0	1.0	0.29%	0.10%
F	5.0	9.0	0.49%	0.88%	1.0	1.0	0.10%	0.10%
G	1.0	0.0	0.10%	0.00%	1.0	0.0	0.10%	0.00%
EE	1.0	0.0	0.10%	0.00%	0.0	0.0	0.00%	0.00%
Total	11.0	10.0	1.08%	0.98%	5.0	2.0	0.49%	0.20%

Code E: IS Variation

Code F: Response in predose sample

Code G: Poor Chromatography

Code EE: Repeat of repeats

Study Code: : LBC-13-081 Fed Study Analyte: Iloperidone								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.00%	0.00%	0.0	0.0	0.00%	0.00%
E	1.0	0.0	0.11%	0.00%	1.0	0.0	0.11%	0.00%
F	1.0	3.0	0.11%	0.32%	0.0	1.0	0.00%	0.11%
Total	2.0	3.0	0.22%	0.32%	1.0	1.0	0.11%	0.11%

Code E: IS Variation

Code F: Response in predose sample

Study Code: : LBC-13-081 Fed Study Analyte: Iloperidone P88								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.00%	0.00%	0.0	0.0	0.00%	0.00%
E	3.0	0.0	0.32%	0.00%	2.0	0.0	0.22%	0.00%
F	1.0	6.0	0.11%	0.65%	0.0	1.0	0.00%	0.11%
H	1.0	0.0	0.11%	0.00%	1.0	0.0	0.11%	0.00%
Total	5.0	6.0	0.54%	0.65%	3.0	1.0	0.33%	0.11%

Code E: IS Variation

Code F: Response in predose sample

Code H: other un-assignable reason

Table 3. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
LBC-BR024-05	16 Jul 2012	Repeat Sample Analysis

Is there any other particular concern that should be investigated further?	No
--	----

Comments from the Reviewer:

1. There are no PK repeats in both the fasting and fed studies for Iloperidone.
2. The firm provided the documentation in the SOP # LBC-BR024-05 for the above mentioned reasons for reanalysis.
3. Fasting study

Parent drug Iloperidone as analyte:

There are a total of 15 samples repeated for reasons of Sample concentration exceeding ULOQ (Code D) (1), IS Variation (Code E) (3), Response in predose sample (Code F) (10), and Poor Chromatography (Code G) (1).

(b) (4)

(b) (4)



5. The reviewer considers all the repeats are acceptable.

3.6 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested, if applicable	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Waiver regulation cited?	21 CFR § 320.22(d)(2)
Strengths considered for 21 CFR 320.24 (b)(6)	N/A
Proportional to strength tested in vivo?	Yes (Please see details in Appendix 4.2 Formulation Data).
Is dissolution acceptable?	Yes
Waivers granted?	WAIVERS GRANTED
If not then why?	N/A

3.7 Deficiency Comments

None

3.8 Comments for Other OGD Disciplines

Discipline	Comment
None	

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4. Study Information

Study Number	ILOP-1K-569-13/ LBC-13-080
Study Title	An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of Iloperidone Tablets 1 mg of Lupin limited, India and Fanapt® (Iloperidone) Tablets 1 mg (b) (4) Distributed by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 in healthy, adult, human male subjects under fasting conditions.
Study Type	☒ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other (Specify)
Submission Location:	m 5.3.1.2
Study Report	m5.3.1.4
Validation Report	m5.3.1.4
Bioanalytical Report	m5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Micro Therapeutic Research Labs Private Limited, No.6, Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059. Tamil Nadu, India. Phone: +91 44 22390070 – 72. Fax : +91-44-22390068
Principal Clinical Investigator (Name, Email)	Dr. D. Sridevi Muthusivam, M.B.B.S, PGDCR, MHSC, (DIAB), E-mail: sridevi.d@microtheraps.com
Dosing Dates	Period I – 19 Mar 13 Period II – 29 Mar 13
Analytical Site (Name, Address, Phone #, Fax #)	Lupin Bioresearch Center, Sai Trinity A Wing, Unit 1, 2, 3 & 4, Survey No. 146/2/1B, Pashan, Pune – 411021, Maharashtra, India Ph.: +91-20-66219200 Fax: +91-20-66219224
Analysis Dates	Start Date: 17 Apr 2013 End Date: 24 Apr 2013
Principal Analytical Investigator (Name, Email)	Mr. Sukhadev Pawar, M.Sc. E-mail: sukhadevpawar@lupinpharma.com
Sample Storage:	
a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)	36 days -30°C ± 05°C
b) Temperature	

range	
-------	--

Table 5. Product information

Product	Test	Reference
Treatment ID	T	R
Product Name	Iloperidone Tablets 1 mg	Fanapt® (Iloperidone) Tablets 1 mg
Manufacturer	Lupin Limited, Goa, India	(b) (4) Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936
Batch No./Lot No.	G390074 [#]	FFZN
Manufacture Date	Jan.2013	Not available
Expiration Date	Dec.2014	Apr 2014
Strength	1 mg	1 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	Not applicable
Production Batch Size	Not applicable	Not applicable
Potency	1.00 mg/tablet (100.0 % of label claim)	1.00 mg/tablet (100.0 % of label claim)
Content Uniformity (mean, %CV)	5.2 %	Not available
Dose Administered	3 x 1 mg	3 x 1 mg
Route of Administration	Single dose, Oral	Single dose, Oral

[#] Batch number G390074 is for 60's HDPE Bottle pack used in the bioequivalence (BE) studies and accordingly reflected in all BE study and related documents. It is noted that the parent batch is G390057.

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	N/A
---	-----

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 34 (inclusive of 02 standby subjects) Dosed: Period-I: 32; Period-II: 28 Completed: 28 Samples Analyzed: 30 Data Analyzed: 28
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	10 days

ANDA 206890
Single-Dose Fasting Bioequivalence Study Review

Randomization Scheme (Sequence of T and R)	Yes
Blood Sampling Times	A total of 18 blood samples were collected at 00.00 (pre-dose), 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00 and 96.00 hours post dose.
Blood Sample Processing & Storage (include storage temperature)	Blood samples were collected via indwelling cannula in K2EDTA vacutainers. Collected blood samples were placed in thermo-insulated box containing ice packs until centrifugation. The plasma was separated by centrifuging at 3800 RPM for 10 minutes at 10°C. Centrifugation process was started within 30 minutes of blood sample collection. Separated plasma samples were transferred to pre-labeled polypropylene tubes into two aliquots (aliquot I & aliquot II). At each time point the separated plasma aliquots were transferred into freezer and stored at a temperature $-30^{\circ}\text{C} \pm 05^{\circ}\text{C}$ in the clinical site until transfer to the bio analytical facility. After completion of the clinical phase, plasma samples were transferred to analytical site (Lupin Bioresearch Center, Pune) at $-75^{\circ}\text{C} \pm 10^{\circ}\text{C}$ in a thermo insulated box containing sufficient dry ice to maintain integrity of the samples throughout the duration of transport. Samples upon receipt were stored in Deep Freezer [LBC-DF-006] at $-30.0 \pm 5^{\circ}\text{C}$ at Bioanalytical Research Department of LBC.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

(Study No.: ILOP-1K-569-13/ LBC-13-080)			
		Treatment Groups	
		Test Product (N = 28)	Reference Product (N = 28)
Age (years)	Mean ±SD Range	28.68 ± 5.70 (21.00 -39.00)	28.68 ± 5.70 (21.00 -39.00)
Age Groups	< 18	00 (00.00 %)	00 (00.00 %)
	18 – 40	28 (100.00%)	28 (100.00%)
	41 – 64	00 (00.00 %)	00 (00.00 %)
	65 – 75	00 (00.00 %)	00 (00.00 %)
	> 75	00 (00.00 %)	00 (00.00 %)
Sex	Male	28 (100 %)	28 (100 %)
	Female	00 (00.00 %)	00 (00.00 %)
Race	Asian	28 (100 %)	28 (100 %)
	Black	00 (00.00 %)	00 (00.00 %)
	Caucasian	00 (00.00 %)	00 (00.00 %)
	Hispanic	00 (00.00 %)	00 (00.00 %)
	Other	00 (00.00 %)	00 (00.00 %)
BMI	Mean ± SD Range	22.23 ± 2.18 (18.67 - 24.98)	22.23 ± 2.18 (18.67 - 24.98)
Other Factors	Nil		

Table 8. Dropout Information, Fasting Bioequivalence Study

(Study No. ILOP-1K-569-13/ LBC-13-080)				
Subject ID.	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	Withdrawn after dosing due to adverse event	I	No	N/A
	Not reported to the facility	II	No	N/A
	Not reported to the facility	II	No	N/A
	Withdrawn after dosing due to adverse event	I	No	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups (%)	
	Fasting Bioequivalence Study (Study No.: ILOP-1K-569-13/ LBC-13-080)	
	TEST	REFERENCE
Cardiac disorders / Giddiness	20.69 % (06)	9.68 % (03)
Cardiac disorders / Syncope	N/A	3.23 % (01)*
Gastro intestinal disorders/ Vomiting	3.45 % (01)	N/A
Total	24.14 % (07)	12.91 % (04)

*Per the RLD labeling, FANAPT can cause dizziness, tachycardia, syncope, nausea, etc.⁴

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Time Post-Dose (24 hour time)	Duration Between Dosing and Emesis (min)
(b) (6)	Test	I	12:10	250

⁴ DRUGS@FAD, search term: Fanapt, last accessed on May, 2015.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022192s013lbl.pdf

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Yes. There are 6 and 3 incidences of giddiness reported for the test and RLD treatments, respectively. One incidence of syncope was reported for the reference treatment and one incidence of vomiting for the test treatment. All these types of adverse events (AEs) are included as common AEs in the RLD labeling.

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee?

None. The one incidence of syncope from the reference treatment was reported by the firm as mild in severity. In addition, the RLD labeling indicates that this drug product can cause syncope.

Are there any other safety concerns based on the adverse event profile?

None

Table 10. Protocol Deviations, Fasting Bioequivalence Study

(Study No. ILOP-1K-569-13/ LBC-13-080)			
S. No.	Type	Subject ID (Test)	Subject ID (Reference)
01	As per section 15.2 and 15.3 of the protocol, post study assessments (ECG and lab assessment) could not be performed for subject no. (b) (6). Because the subject did not report to the facility for Period II of the study. However, the well-being & safety of both the subject was confirmed over telephonic contact. It has been concluded to have no impact on the overall outcome of the study	Not applicable	Not applicable

Comments:

1. A total of 34 subjects were enrolled in the study. Twenty-eight (28) out of 32 dosed subjects completed the study. Subject no. (b) (6) dropped out of the study due to adverse event in Period-I. Subject no. (b) (6) dropped out of the study because they did not report to the facility for Period II check-in. The reviewer verified these dropouts from the case report forms (CRFs).

2. A total of eleven (11) adverse events were reported in the study. Of the eleven (11) adverse events seven (07) were reported after administration of the test product and four (04) were reported after administration of the reference product. All the adverse events were found to be mild in intensity but considered as related to the administration of study products. All adverse events were resolved on the same day without any sequelae. There were no serious adverse events or deaths reported in the study. Per the RLD labeling, the commonly observed adverse reactions (incidence $\geq 5\%$ and 2-fold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, nausea and weight increased, etc. All the observed adverse events are included in the RLD labeling.
 - Subject no. (b) (6) experienced an adverse event of “vomiting” 250 minutes post-dose in Period I. The event was “mild” in intensity but considered as related to the administration of the test product. The onset of emesis was outside 2 times of the median T_{max} of the test product ($2 \times 2.00 \times 60 = 240$ min) in the fasting study. The adverse event was treated with IV injection of Emeset (Ondansetron) and the event was completely resolved on the same day without any sequelae. The subject was withdrawn from the study. The reviewer considers that the vomiting and the concomitant medication had no impact to the PK study outcome since the subject was withdrawn from the study in period I and was not included in the data analysis. .
 - Subject no. (b) (6) experienced an adverse event of “Syncope” post-dose in Period I. The event was “mild” in intensity but considered as related to the administration of the reference product. The adverse event was treated with concomitant medication of IV injection of sodium lactate and was completely resolved on the same day without any sequelae. The subject was withdrawn from the study due to the adverse event. The reviewer considers that the adverse event and the concomitant medication had no impact to the PK study outcome since the subject didn’t complete the study and was not included in the data analysis.
3. There was one (1) protocol deviation. As per protocol, ECG was recorded at the time of check-out (ECG) of Period II for all the subjects except subject no. (b) (6) who did not report to the facility for Period II. Sample for post study safety assessment was collected at the time of 96.00 hours post dose of Period II for all subjects except for Subject no. (b) (6) who did not report to the facility for Period II check-in. The reviewer considers that this protocol deviation had no impact on the overall outcome of the study since the subject didn’t complete the study and was not included in the data analysis.

4.1.1.3 Bioanalytical Results

Table 11. Sample Analysis Calibration and Quality Control

Bioequivalence Study Code: LBC-13-080 Fasting Study Analyte: Iloperidone								
Parameter	Standard Curve Samples							
	CS 8	CS 7	CS 6	CS 5	CS 4	CS 3	CS 2	CS 1
Concentration (pg/ml)	10046.32 8	8237.98 9	6178.49 2	4121.05 4	2060.52 7	1030.26 4	201.41 7	100.70 8
Inter day Precision (% CV)	2.86	2.82	2.74	1.95	3.20	3.58	11.22	2.51
Inter day Accuracy (% Actual)	97.66	98.89	100.20	99.62	100.98	103.67	99.01	100.29
Linearity (r)	0.997548-0.999966							
Linearity Range (pg/ml)	100.708-10046.328							
Sensitivity/LLO Q (pg/ml)	100.708							

Bioequivalence Study Code: LBC-13-080 Fasting Study Analyte: Iloperidone			
Parameter	Quality Control Samples		
	HQC	MQC	LQC
Concentration (pg/ml)	7120.796	4130.062	276.714
Inter day Precision (%CV)	7.01	5.12	13.56
Inter day Accuracy (%Actual)	95.82	96.59	99.93

Bioequivalence Study Code: LBC-13-080 Fasting Study Analyte: Iloperidone P88								
Parameter	Standard Curve Samples							
	CS 8	CS 7	CS 6	CS 5	CS 4	CS 3	CS 2	CS 1
Concentration (pg/ml)	10015.92 2	8213.05 6	6159.79 2	4108.58 1	2054.29 1	1027.14 5	200.80 7	100.40 3
Inter day Precision (%)	1.99	2.72	1.73	1.98	2.78	4.03	6.07	2.87
Inter day Accuracy (%)	97.78	97.69	98.80	99.89	101.18	104.58	101.09	99.05
Linearity (r)	0.997072-0.999826							
Linearity Range (pg/ml)	100.403-10015.922							

ANDA 206890
Single-Dose Fasting Bioequivalence Study Review

Sensitivity/LLO Q (pg/ml)	100.403
------------------------------	---------

Bioequivalence Study Code: LBC-13-080 Fasting Study Analyte: Iloperidone P88			
Parameter	Quality Control Samples		
	HQC	MQC	LQC
Concentration (pg/ml)	7099.638	4117.790	275.892
Inter day Precision (%CV)	7.98	7.17	11.17
Inter day Accuracy (%Actual)	96.01	97.71	99.70

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Are there any concerns related to sample analysis (including reanalysis, run rejection, etc.)?	No

Were 20% of chromatograms included?	Yes (Subjects (b) (6))
Did the firm provide 100% numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log) in the instrument printout format?	Yes

Table 12. SOP's Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
AAP-13-014-00	04/15/2013	Estimation of Iloperidone and Iloperidone P88 in Human Plasma using UPLC-MS/MS
LBC-BR024-05	07/16/2012	Repeat Sample Analysis
LBC-BR023-03	09/11/2012	Study Sample Analysis and Analytical Run Acceptance Criteria
LBC-BR025-02	11/21/2011	Incurred Sample Reanalysis
LBC-BROI4-02	11/02/2012	Assessment of Quality of Chromatogram

Comments:

1. For ISR, 116 out of 1022 total analyzed samples (11.35%) for both Iloperidone and Iloperidone P88 were reanalyzed. The results are listed in the tables below. The variability of 93.58% and 98.16% of reanalyzed samples are acceptable for Iloperidone and Iloperidone P88, respectively. Per acceptance criteria in the SOP # LBC-BR025-02 that the percentage difference of the original and repeat values must be within $\pm 20\%$. And 75% of the total incurred samples analyzed (irrespective of the number of analytical batches) must meet the criteria. Therefore, the assay is considered reproducible.

• **Summary of Incurred sample Reanalysis for Iloperidone**

No. of samples analysed	116
No. of samples rejected due to analytical reason	07 (IS variation)
No. of valid ISR samples	109
No. of failed ISR samples	07
No. of passed ISR samples	102
Percentage of the within acceptance criteria (%)	93.58%

• **Summary of Incurred sample Reanalysis for Iloperidone P88**

No. of samples analysed	116
No. of samples rejected due to analytical reason	07 (IS variation)
No. of valid ISR samples	109
No. of failed ISR samples	02
No. of passed ISR samples	107
Percentage of the within acceptance criteria (%)	98.16%

4.1.1.4 Pharmacokinetic Results

Table 13. Arithmetic Mean Pharmacokinetic Parameters

Iloperidone-Firm Calculated																
PK parameter (Units)	N	Mean		SD		Min		Median		Max		CV%		Geometric Mean		Ratio
		T	R	T	R	T	R	T	R	T	R	T	R	T	R	
T _{max} (hr)	28	2.071	1.839	0.802	0.695	1.00	1.00	2.00	2.00	4.00	3.50	38.71	37.76	1.936	1.721	100
C _{max} (pg/mL)	28	4012.3215	3948.7021	2339.4344	1755.6714	1249.713	1291.962	3703.851	3754.112	11381.658	1541.518	58.31	44.46	3476.0135	3536.5028	101.61
AUC _{0-t} (pg*hr/mL)	28	57322.2177	56901.1610	35670.1232	28345.3230	23737.332	23495.310	44227.039	47837.298	192677.874	142689.321	62.23	49.82	50175.8031	51206.6046	100.74
AUC _{0-∞} (pg*hr/mL)	28	64259.0917	63135.0795	39048.9106	30477.2113	27474.179	30029.683	49241.359	53140.674	210054.850	157981.565	60.77	48.27	56590.3680	57423.3537	101.78
K _{el} (hr ⁻¹)	28	0.0300	0.0305	0.0109	0.0091	0.017	0.019	0.028	0.031	0.058	0.055	36.18	29.75	0.0283	0.0293	
t _{1/2} (hr)	28	25.786	24.606	8.199	6.922	12.04	12.65	25.16	22.73	41.27	37.20	31.80	28.13	24.465	23.660	
AUC _{%Extrap_{obs}} (%)	28	11.2225	10.6808	4.4942	5.0597	4.176	4.413	10.878	10.406	21.807	25.312	40.05	47.37	10.3725	9.6551	

Iloperidone P88-Firm Calculated																
PK parameter (Units)	N	Mean		SD		Min		Median		Max		CV%		Geometric Mean		Ratio
		T	R	T	R	T	R	T	R	T	R	T	R	T	R	
T _{max} (hr)	28	2.964	2.571	1.178	1.034	1.50	1.00	2.75	2.00	6.00	4.00	39.74	40.20	2.737	2.372	138
C _{max} (pg/mL)	28	3919.3668	3969.5012	1589.6558	1807.7351	1456.406	1438.866	3718.251	3828.914	8832.838	9832.615	40.56	45.54	3641.4297	3649.7295	98.74
AUC _{0-t} (pg*hr/mL)	28	95767.5912	93640.5203	46070.2323	43164.9390	29022.212	20365.727	87837.694	89312.451	280103.971	264201.840	48.11	46.10	87424.4597	85422.9151	102.27
AUC _{0-∞} (pg*hr/mL)	28	114284.3659	104049.3895	59788.2166	50834.6194	51830.205	23971.749	98299.258	98728.735	323664.454	311635.487	52.32	48.86	103581.6922	94501.4843	109.83
K _{el} (hr ⁻¹)	28	0.0251	0.0253	0.0075	0.0077	0.000	0.017	0.024	0.023	0.040	0.048	30.03	30.45	0.0220	0.0244	
t _{1/2} (hr)	28	83.400	29.303	293.713	6.751	17.31	14.43	29.08	29.60	1581.80	41.09	352.17	23.04	31.560	28.443	
AUC _{%Extrap_{obs}} (%)	28	11.7743	9.5569	15.4283	3.0569	3.180	3.992	8.558	9.116	89.079	15.221	131.03	31.99	9.1326	9.0423	

Reviewer's note: The reviewer noted that one of the t_{1/2} (max) (Subject (b) (6)) for Iloperidone P88 is 1581.80 hr for the test product, which is very different from the rest of the values in the study. And in turn the AUC_{%Extrap} is 89.079%. The reviewer noted that the firm used the last three time points (Best fit) to calculate the t_{1/2}, which are flat (105.9381, 104.795, and 103.733 pg/mL). The reviewer included the time point from 6.00 hr to 96.00 hr for the fitting and recalculated the PK parameters in Phoenix and the results are listed in the table below.

ANDA 206890
Single-Dose Fasting Bioequivalence Study Review

Iloperidone-Reviewer Calculated																
PK parameter (Units)	N	Mean		SD		Min		Median		Max		CV%		Geometric Mean		Ratio
		T	R	T	R	T	R	T	R	T	R	T	R	T	R	
T _{max} (hr)	28	2.1	1.8	0.8018	0.6946	1.0	1.0	2.0	2.0	4.0	3.5	38.7	37.8	1.9	1.7	100
C _{max} (pg/mL)	28	4012.32	3948.70	2339	1756	1249.7	1292.0	3703.9	3754.1	11381.7	7541.5	58.3	44.5	3476.01	3536.50	101.61
AUC _{0-t} (pg*hr/mL)	28	57566.98	57115.85	35825	28461	24049.4	23904.1	44665.5	48100.4	193797.6	143542.3	62.2	49.8	50409.90	51416.46	100.79
AUC _{0-∞} (pg*hr/mL)	28	64379.24	63321.12	39107	30490	27894.0	30453.4	49721.8	53299.4	211223.4	158866.5	60.7	48.2	56755.98	57643.28	101.67
K _{el} (hr ⁻¹)	28	0.030162	0.030425	0.010087	0.008755	0.017229	0.019129	0.027811	0.030562	0.055775	0.054573	33.4	28.8	0.028695	0.029299	
t _{1/2} (hr)	28	25.3	24.5	7.690	6.608	12.4	12.7	24.9	22.7	40.2	36.2	30.4	26.9	24.2	23.7	
AUC _{%Extrap_{obs}} (%)	28	11.1	10.7	4.463	5.112	4.2	4.4	11.0	10.4	21.9	25.5	40.3	48.0	10.2	9.6	

Iloperidone P88-Reviewer Calculated																
PK parameter (Units)	N	Mean		SD		Min		Median		Max		CV%		Geometric Mean		Ratio
		T	R	T	R	T	R	T	R	T	R	T	R	T	R	
T _{max} (hr)	28	3.0	2.6	1.178	1.034	1.5	1.0	2.75	2.0	6.0	4.0	39.7	40.2	2.7	2.4	138
C _{max} (pg/mL)	28	3919.4	3969.5	1590	1808	1456.4	1438.9	3718.3	3828.9	8832.8	9832.6	40.6	45.5	3641.4	3649.7	98.74
AUC _{0-t} (pg*hr/mL)	28	96099.0	93902.7	46162	43173	29165.7	20382.0	87980.7	89596.1	280613.1	264201.8	48.0	46.0	87743.87	85680.7	102.34
AUC _{0-∞} (pg*hr/mL)	28	106151.5	104057.6	53791	50847	32963.4	24403.0	97423.7	97106.7	323733.6	311635.5	50.7	48.9	96347.9	94555.4	102.01
K _{el} (hr ⁻¹)	28	0.026162	0.025535	0.005508	0.006580	0.017253	0.017726	0.025264	0.024125	0.039960	0.047925	21.1	25.8	0.025636	0.024871	
t _{1/2} (hr)	28	27.6	28.5	5.480	5.770	17.3	14.5	27.4	28.7	40.2	39.1	19.9	20.2	27.0	27.9	
AUC _{%Extrap_{obs}} (%)	28	8.89	9.34	2.817	3.015	3.15	3.99	8.25	8.99	13.58	16.48	31.69	32.3	8.41	8.85	

Table 14. Summary of Geometric Least Square Mean, Ratios and 90% Confidence Interval

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Iloperidone

PK Parameter	N	Geometric Least Square Means		T/R Ratio (%)	90% Confidence Interval		ISCV (%)
		Test (T)	Reference (R)		LCL	UCL	
C _{max} (pg/mL)	28	3510.8062	3504.0978	100.19	93.59	107.26	14.95
AUC _{0-t} (pg*hr/mL)	28	50425.3797	51239.4368	98.41	94.71	102.25	8.40
AUC _{0-∞} (pg*hr/mL)	28	56927.1901	57485.7671	99.03	95.06	103.17	8.98

N-Number of Observations

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for the active P88 metabolite

PK Parameter	N	Geometric Least Square Means		T/R Ratio (%)	90% Confidence Interval		ISCV (%)
		Test (T)	Reference (R)		LCL	UCL	
C _{max} (pg/mL)	28	3633.9882	3612.0581	100.61	95.12	106.41	12.30
AUC _{0-t} (pg*hr/mL)	28	87082.4343	84788.7799	102.71	98.79	106.77	8.52
AUC _{0-∞} (pg*hr/mL)	28	103740.096	93753.9542	110.65	95.49	128.23	32.34

N-Number of Observations

Iloperidone-Reviewer Calculated							
PK Parameter	N	Geometric Least Square Mean		T/R Ratio (%)	90% Confidence Interval		Power_80
		T	R		LCI	UCI	
Ln(Cmax)	28	3510.8	3504.1	100.19	93.57	107.28	0.9997
Ln(AUC0-t)	28	50662.2	51453.9	98.46	94.78	102.28	1.0000
Ln(AUC0-∞)	28	57097.5	57710.5	98.94	95.01	103.03	1.0000

Iloperidone P88-Reviewer Calculated							
PK Parameter	N	Geometric Least Square Mean		T/R Ratio (%)	90% Confidence Interval		Power_80
		T	R		LCI	UCI	
Ln(Cmax)	28	3634.0	3612.1	100.61	95.11	106.42	1.0000
Ln(AUC0-t)	28	87402.4	85046.6	102.77	98.86	106.84	1.0000
Ln(AUC0-∞)	28	95962.4	93825.5	102.28	98.49	106.21	1.0000

Reviewer's note: The reviewer noted from the firm's summary table above that the 90% CI of the AUC_{0-∞} for Iloperidone P88 doesn't meet the acceptance limit of 80.00-125.00% because AUC_{0-∞} value of subject (b) (6) of the test product was very high (265746.021 pg/mL*hr), and the T/R ratio was 11.08. The reviewer checked the firm's PK data and noted that the t_{1/2 (max)} of Subject (b) (6) for Iloperidone P88 is 1581.80 hr for the test product, which is very different from the rest of the values from the study. And in turn the AUC%_{Extrap} is 89.079%. The reviewer noted that the firm used the last three time points (Best fit) to calculate the t_{1/2}, which are flat (105.9381, 104.795, and 103.733 pg/mL). The reviewer considers that the firm's fitting not appropriate for this subject. The reviewer included the time point from 6.00 hr to 96.00 hr for the fitting as shown in the plot below and recalculated the PK parameters in Phoenix. The reviewer then reconducted the BE statistical analysis for Iloperidone P88. The 90% confidence intervals for iloperidone P88 of lnAUC_{0-t}, lnAUC_{0-∞} and lnC_{max} of the test product are all within the acceptance limit of 80.00-125.00% of the reference product as per the reviewer's calculation as shown in the table above.

ANDA 206890
Single-Dose Fasting Bioequivalence Study Review



Is there a Tmax difference between T and R	–Iloperidone: The median Tmax is the same between test product and reference product (2.00 hr). The median Tmax is 2-4 hrs per the RLD labeling. –Iloperidone P88: The median Tmax for the test product and reference product are 2.75 hr and 2.00 hr for T and R, respectively. The T/R ratio is 1.38.
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Sampling time is adequate. The reviewer verified that the AUC _{0-t} /AUC _{0-∞} ratios of all the subjects but 4 are > 80.00% for Iloperidone.

Reviewer's note: A total of 4 subjects (two for the test product, two for the reference product) had AUC_{0-t}/AUC_{0-∞} ratios below 80.00% in terms of Iloperidone but the differences are small as shown in the table below. The reviewer also checked the semi-log plasma concentration time profiles for these subjects and the sampling schedule has adequately captured the elimination phase for all these subjects. The average AUC_{0-t}/AUC_{0-∞} ratios of T and R are 88.8% and 89.3%, respectively. Therefore, the reviewer considers that the sampling time is adequate.

Subject	Treatment	Period	AUC _{0-t} /AUC _{0-∞} ratio
(b) (6)	R	I	74.5
	R	I	76.5
	T	I	78.2
	T	II	79.3

Overall Comment:

1. The median Tmax is the same between the test product and the reference product (2.00 hrs) for iloperidone. Per RLD labeling, median Tmax is 2-4 hours, where

the median Tmax for the test product and reference product in the current application fell within. For iloperidone P88, the median Tmax is different between the test product (2.75 hrs) and the reference product (2.00 hrs) with the ratio (T/R) of 1.38. The variability as determined by CV% was comparable for Test product (39.7%) and Reference product (40.2%) for iloperidone P88.

2. The reviewer also did an in-house survey on the available ANDA applications of the same drug product in DARRTS for Tmax data under fasting conditions for iloperidone P88 and the results are listed in the table below. The reviewer noted that among the in-house ANDAs of Iloperidone Tablets, the median Tmax of iloperidone P88 ranged from 2.75 hours to 4.00 hours for the test product and from 2.00 hours to 4.50 hours for the reference product, with the Min-Max range at the most of 1.33 hours-10.00 hours. The reviewer considers that the median Tmax of iloperidone P88 in the current BE study under fasting condition is not stood out of the median Tmax in other ANDAs of the same drug product.

Tmax (range) (hr)	Current ANDA	ANDA 207098 (Pending)*	(b) (4)	ANDA 207409 (Pending)*	(b) (4)
Test	2.75 (1.50- 6.00)	3.75 (2.00- 6.00)		4.00 (2.00- 8.00)	
Reference	2.00 (1.00- 4.00)	3.50 (2.00- 4.50)		4.50 (1.00- 8.00)	

*As of 5/11/2015, BE review is pending.

3. As per the current DB policy, the firm's statistical analyses were evaluated by the reviewer. Based on the firm's calculation, the 90% confidence intervals for iloperidone of $\ln AUC_{0-t}$, $\ln AUC_{0-\infty}$ and $\ln C_{max}$ of the test product are within the BE acceptance limits of 80.00-125.00%.
4. The pharmacokinetic (PK) parameters of the test and reference products for the active metabolite P88 are comparable. Therefore, the iloperidone P88 data are supportive.
5. The fasting *in vivo* bioequivalence study is adequate.

Table 15. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study
(Firm-Submitted Data in Firm's Format)
Mean plasma Iloperidone Concentrations (pg /mL) for Test Product

Time (hr)	N	Mean (pg /mL)	SD (pg /mL)	Min (pg /mL)	Max (pg /mL)	CV%
0.00	28	0.0000	0.0000	0.000	0.000	0.00
1.00	28	2201.4920	2350.9019	129.300	11381.658	106.79
1.50	28	3377.3825	2160.6803	369.387	8837.303	63.97
2.00	28	3490.7991	2208.3630	735.324	9230.772	63.26
2.50	28	2977.9315	1885.7494	757.648	8711.126	63.32
3.00	28	2560.2291	1372.8444	723.354	6553.036	53.62
3.50	28	2324.4620	1147.4519	865.761	5787.514	49.36
4.00	28	2178.3051	1019.5592	745.805	5066.071	46.81
6.00	28	1804.2261	937.3360	751.338	5142.907	51.95
8.00	28	1725.3191	845.3911	660.597	4760.404	49.00
10.00	28	1484.8051	846.6962	633.981	4789.859	57.02
12.00	28	1311.3847	745.9982	640.141	4253.269	56.89
16.00	28	971.7036	593.1470	445.183	3434.109	61.04
24.00	28	785.2268	533.5099	380.849	2964.964	67.94
36.00	28	526.0958	378.8705	193.162	2059.607	72.02
48.00	27	380.3011	258.7743	123.674	1383.252	68.04
72.00	28	205.7450	185.6892	0.000	795.609	90.25
96.00	27	89.8447	126.0193	0.000	474.420	140.26

Mean plasma Iloperidone Concentrations (pg /mL) for Reference Product

Time (hr)	N	Mean (pg /mL)	SD (pg /mL)	Min (pg /mL)	Max (pg /mL)	CV%
0.00	28	0.0000	0.0000	0.000	0.000	0.00
1.00	28	2329.0261	1875.2607	161.752	6530.686	80.52
1.50	28	3289.2559	1684.1109	520.842	6559.266	51.20
2.00	28	3459.1055	1729.3305	1291.962	7541.518	49.99
2.50	28	3028.9241	1595.0269	1108.813	7409.653	52.66
3.00	28	2529.8569	1186.6798	968.539	5094.180	46.91
3.50	28	2339.8428	1216.8488	988.612	5203.876	52.01
4.00	28	2242.1663	1178.8075	850.830	4974.003	52.57
6.00	28	1858.7764	828.3879	712.704	3859.407	44.57
8.00	28	1654.4817	743.0037	708.430	3618.745	44.91
10.00	28	1401.7289	651.6085	559.915	3225.721	46.49
12.00	28	1341.0273	662.3858	602.528	3453.468	49.39
16.00	28	927.9897	475.4328	482.805	2546.516	51.23
24.00	28	787.9815	374.7594	335.138	1975.037	47.56
36.00	28	522.4491	309.3189	189.740	1502.834	59.21
48.00	28	371.6399	225.6935	149.344	1096.793	60.73
72.00	28	187.5214	131.5685	0.000	499.323	70.16
96.00	28	94.0399	110.8672	0.000	409.034	117.89

Mean plasma Iloperidone P88 Concentrations (pg /mL) for Test Product

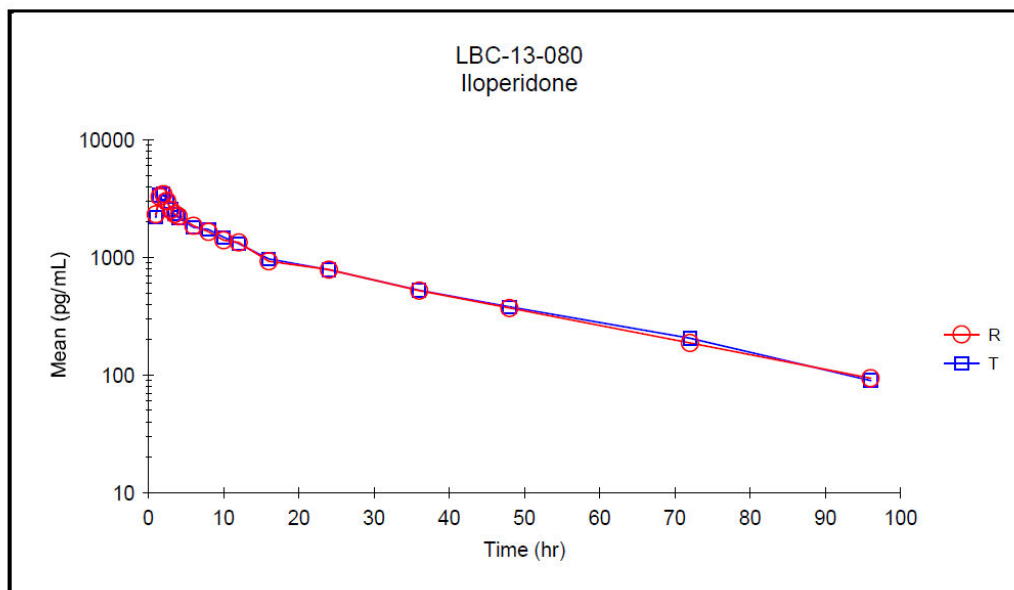
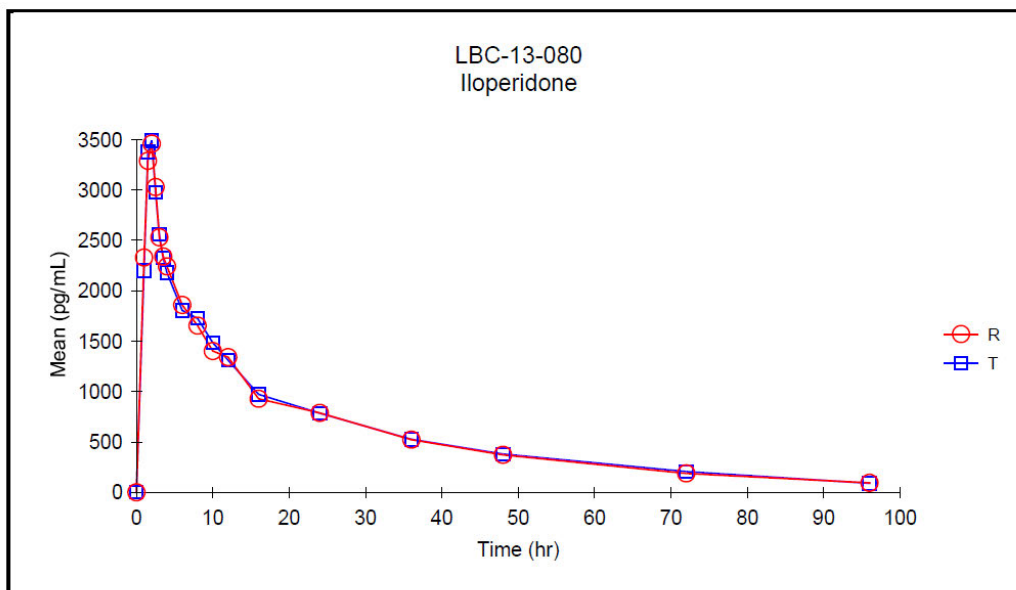
Time (hr)	N	Mean (pg /mL)	SD (pg /mL)	Min (pg /mL)	Max (pg /mL)	CV%
0.00	26	0.0000	0.0000	0.000	0.000	0.00
1.00	28	1712.6889	1477.4438	118.483	5713.741	86.26
1.50	28	3011.4074	1871.2127	267.975	7271.031	62.14
2.00	28	3214.9520	1676.2806	556.510	7382.296	52.14
2.50	28	3307.7456	1432.9806	791.338	7591.482	43.32
3.00	28	3294.7450	1308.6866	1359.687	7803.658	39.72
3.50	28	3297.1842	1443.8068	1303.986	8832.838	43.79
4.00	28	3440.9375	1327.9175	1395.223	8233.000	38.59
6.00	28	2860.6146	1130.7125	764.775	7294.421	39.53
8.00	28	2671.7673	1127.1567	912.773	7384.191	42.19
10.00	28	2385.4461	968.1040	661.363	6004.406	40.58
12.00	28	2194.2386	830.0845	770.772	5155.559	37.83
16.00	28	1766.2931	747.8814	564.901	4640.498	42.34
24.00	28	1463.3616	670.8847	469.278	3915.534	45.85
36.00	28	920.4190	535.2038	273.569	2955.261	58.15
48.00	27	665.0828	437.7553	105.938	2393.263	65.82
72.00	28	368.5737	259.1317	104.795	1430.134	70.31
96.00	27	240.0326	168.8314	102.543	893.829	70.34

Mean plasma Iloperidone P88 Concentrations (pg /mL) for Reference Product

Time (hr)	N	Mean (pg /mL)	SD (pg /mL)	Min (pg /mL)	Max (pg /mL)	CV%
0.00	27	5.1188	26.5981	0.000	138.208	519.62
1.00	28	1910.4083	1639.6075	154.020	7916.785	85.82
1.50	28	3104.6887	1766.9384	541.007	9060.354	56.91
2.00	28	3469.8969	1832.2661	1007.132	9832.615	52.80
2.50	28	3488.9104	1567.8650	1053.974	8795.479	44.94
3.00	28	3358.5088	1523.0516	1121.124	9068.262	45.35
3.50	28	3403.4453	1507.8066	1301.249	9258.433	44.30
4.00	28	3432.4898	1398.1437	1438.866	8378.894	40.73
6.00	28	2873.6771	1128.7305	825.936	7250.501	39.28
8.00	28	2677.9097	1094.9456	965.193	7029.312	40.89
10.00	28	2341.8758	890.5548	544.244	5578.838	38.03
12.00	28	2151.1650	893.9972	483.479	5489.460	41.56
16.00	28	1699.0517	728.0354	268.134	4421.480	42.85
24.00	28	1450.9138	642.0670	506.961	3817.034	44.25
36.00	28	868.6263	449.3331	138.539	2440.800	51.73
48.00	28	603.4237	361.7388	0.000	1973.024	59.95
72.00	28	360.0125	234.7041	119.353	1364.384	65.19
96.00	28	220.6715	164.3138	0.000	840.792	74.46

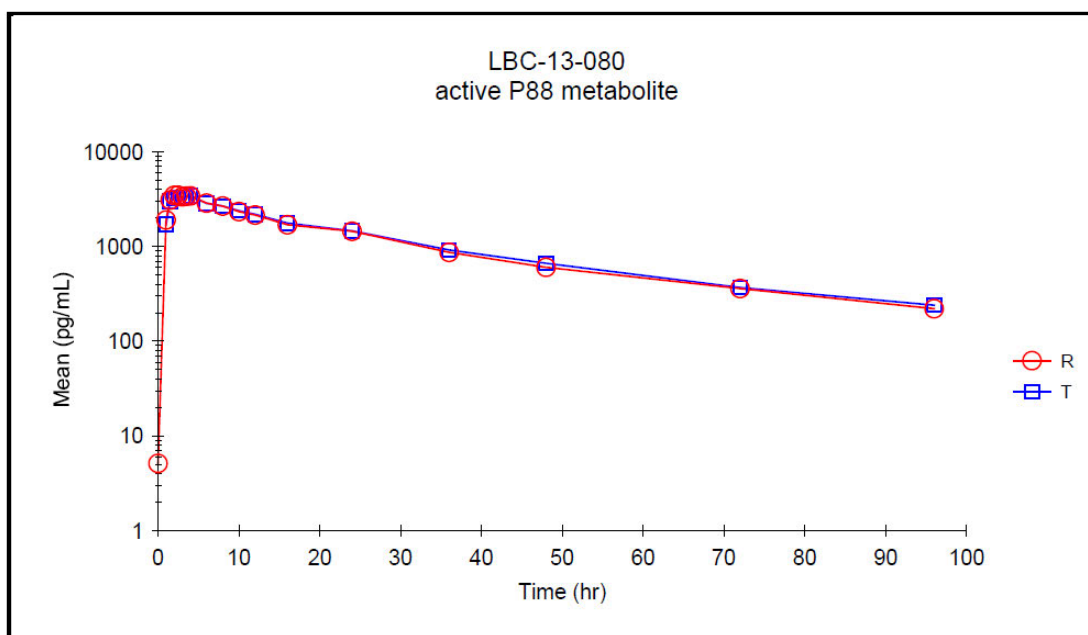
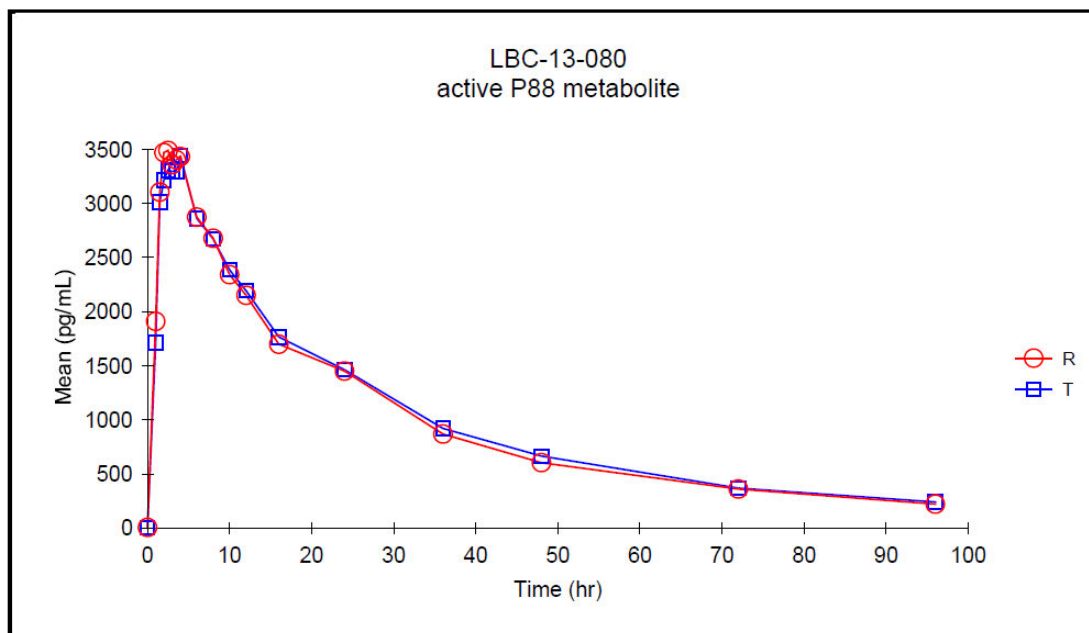
Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study
(Firm-Submitted Plot)

Iloperidone for Test product and Reference product in 28 healthy, adult, human male subjects under fasting conditions



ANDA 206890
Single-Dose Fasting Bioequivalence Study Review

P88 metabolite for Test product and Reference product in 28 healthy, adult, human male subjects under fasting conditions



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 16. Study Information

Study Number	ILOP-1K-570-13/ LBC-13-081			
Study Title	An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of Iloperidone Tablets 1 mg of Lupin limited, India and Fanapt® (Iloperidone) Tablets 1 mg (b) (4) Distributed by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 in healthy, adult, human male subjects under fed conditions.			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other (Specify)
Submission Location: Study Report Validation Report Bioanalytical Report	m 5.3.1.2			
	m5.3.1.4			
	m5.3.1.4			
Clinical Site (Name, Address, Phone #, Fax #)	Micro Therapeutic Research Labs Private Limited, No.6, Kamarajar Salai, Selaiyur, East Tambaram, Chennai - 600 059. Tamil Nadu, India. Phone: +91 44 22390070 – 72. Fax : +91-44-22390068			
Principal Clinical Investigator (Name, Email)	Dr. D. Sridevi Muthusivam, M.B.B.S, PGDCR, MHSC, (DIAB), E-mail: sridevi.d@microtheraps.com			
Dosing Dates	Period I – 20 Mar 13 Period II – 30 Mar 13			
Analytical Site (Name, Address, Phone #, Fax #)	Lupin Bioresearch Center, Sai Trinity A Wing, Unit 1, 2, 3 & 4, Survey No. 146/2/1B, Pashan, Pune – 411021, Maharashtra, India Ph.: +91-20-66219200 Fax: +91-20-66219224			
Analysis Dates	Start Date: 22 Apr 2013 End Date: 28 Apr 2013			
Principal Analytical Investigator (Name,e-mail)	Dr. Niranjan Galpalli, M.Pharm., Ph.D. E-mail: niranjangalpalli@lupinpharma.com			

Table 17. Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Iloperidone Tablets 1 mg	Fanapt® (Iloperidone) Tablets 1 mg (b) (4)
Manufacturer	Lupin Limited, Goa, India	Distributed by: Novartis

ANDA 206890
Single-Dose Fed Bioequivalence Study Review

		Pharmaceuticals Corporation East Hanover, New Jersey 07936
Batch No./Lot No.	G390074 [#]	FFZN
Manufacture Date	Jan.2013	Not available
Expiration Date	Dec.2014	Apr 2014
Strength	1 mg	1 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	Not applicable
Production Batch Size	Not applicable	Not applicable
Potency	1.00 mg/tablet (100.0 % of label claim)	1.00 mg/tablet (100.0 % of label claim)
Content Uniformity (mean, %CV)	5.2 %	Not available
Dose Administered	3 x 1 mg	3 x 1 mg
Route of Administration	Single dose, Oral	Single dose, Oral

[#] Batch number G390074 is for 60's HDPE Bottle pack used in the bioequivalence (BE) studies and accordingly reflected in all BE study and related documents. It is noted that the parent batch is G390057.

Was the drug product administered per labeling?	No.
--	-----

Table 18. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 34 (Inclusive of 2 standby subjects) Dosed: Period-I: 32; Period-II: 29 Completed: 29 Samples Analyzed: 29 Data Analyzed: 29
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	10 days
Randomization Scheme (Sequence of T and R)	Yes
Blood Sampling Times	In each period, a total of 16 blood samples were collected at 00.00 (pre-dose), 01.00, 02.00, 03.00, 04.00, 5.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00 and 96.00 hours.

ANDA 206890
Single-Dose Fed Bioequivalence Study Review

Blood Sample Processing & Storage (include storage temperature)	Blood samples were drawn using sterile, disposable syringes from indwelling intravenous cannula placed in the cubital fossa and transferred into pre-labelled K2EDTA vacutainers. Collected blood samples were placed in thermo-insulated box containing wet ice until centrifugation.. Blood samples were centrifuged at 3800 rpm for 10 minutes at 10°C to separate the plasma. Centrifugation process was started within 30 minutes of blood sample collection. Separated plasma samples were transferred to pre-labeled polypropylene tubes into two aliquots (aliquot I & aliquot II) for bioanalysis of Iloperidone and the active P88 metabolite. At each time point the separated plasma aliquots were stored in a freezer at a temperature -30°C ± 05°C in the clinical site until transfer to the bio analytical facility. After completion of the clinical phase, plasma samples were transferred to analytical site (Lupin Bioresearch Center, Pune) at -75°C ± 10°C in a thermo insulated box containing sufficient dry ice to maintain integrity of the samples throughout the duration of transport. Pharmacokinetic and statistical analyses were performed on obtained drug concentration data at Lupin Bioresearch Center, Pune. Samples upon receipt were stored in Deep Freezer [LBC-DF-006] at -30.0 ± 5°C at Bioanalytical Research Department of LBC.
--	---

Standard FDA Meal Used?	No
--------------------------------	----

Composition of Meal Used in Fed Bioequivalence Study

Composition of Meal Used in Fed Bioequivalence Study					
Standard FDA Meal Used?		☐ Yes ☒ No			
If No, then meal components and composition is listed in the tables below					
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study					
Ingredients	Amount (g)	Energy (Kcal)	Protein (kcal)	Fat (kcal)	Carbohydrate (kcal)
Bread	40 g (2 Slices)	98.04	12.48	2.52	83.04
Butter	5 g	36.45	-	36.45	-
Egg	2 No's (50 g App. Each)	172.9	53.2	119.7	-
Onion	5 g	2.485	0.24	0.045	2.2
Oil	5 g	45	-	45	-
Ghee	7g	63	-	63	-
Coriander leaves	few	-	-	-	-
Potato	30 g	29.31	1.92	0.27	27.12
Ginger	5 g	3.24	0.44	0.36	2.44
Onion	10 g	5.01	0.48	0.09	4.44
Oil	12 g	108.0	-	108.0	-
Cheese	20 g	69.5	19.28	45.18	5.04
Chicken	40 g	43.6	41.44	2.16	-
Ginger	5 g	3.24	0.44	0.36	2.44
Onion	5 g	2.485	0.24	0.045	2.2
Oil	10 g	90	-	90	-
Milk	250 ml	168.25	32	92.25	44
Sugar	15 g	59.68	0.04	-	59.64

ANDA 206890
Single-Dose Fed Bioequivalence Study Review

TOTAL	N/A	1000.19	162.2	605.43	232.56
PERCENTAGE	N/A	100.00	16.22	60.53	23.25

Comments on Study Design:

Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies (December 2002) states that “*A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively*”.⁵ The firm did not use the Standard FDA Meal (two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk). However, the modified high-fat breakfast meal the firm used provided about 162.2, 232.56, and 605.43 calories from protein, carbohydrate, and fat, respectively, which is consistent with the guidance recommendation.

The study design is acceptable.

⁵ The Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies (recommended in 12/2002)

4.1.2.2 Clinical Results

Table 19. Demographics Profile of Subjects Completing the Bioequivalence Study

(Study No.: ILOP-1K-570-13/ LBC-13-081)			
		Treatment Groups	
		Test Product (N = 29)	Reference Product (N = 29)
Age (years)	Mean $\pm$ SD Range	29.21 $\pm$ 5.46 (20.00 -42.00)	29.21 $\pm$ 5.46 (20.00 -42.00)
Age Groups	< 18	00 (00.00 %)	00 (00.00 %)
	18 – 40	27 (93.10%)	27 (93.10%)
	41 – 64	02 (06.89 %)	02 (06.89 %)
	65 – 75	00 (00.00 %)	00 (00.00 %)
	> 75	00 (00.00 %)	00 (00.00 %)
Sex	Male	29 (100 %)	29 (100 %)
	Female	00 (00.00 %)	00 (00.00 %)
Race	Asian	29 (100 %)	29 (100 %)
	Black	00 (00.00 %)	00 (00.00 %)
	Caucasian	00 (00.00 %)	00 (00.00 %)
	Hispanic	00 (00.00 %)	00 (00.00 %)
	Other	00 (00.00 %)	00 (00.00 %)
BMI	Mean $\pm$ SD Range	22.44 $\pm$ 2.07 (18.65 - 24.86)	22.44 $\pm$ 2.07 (18.65 - 24.86)
Other Factors	Nil		

Table 20. Dropout Information, Fed Bioequivalence Study

(Study No. ILOP-1K-570-13/ LBC-13-081)				
Subject ID.	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	Withdrawn from the study due to failure in complying with restrictions and prohibitions	II	No	N/A
	Not reported to the facility	II	No	N/A
	Withdrawn from the study due to personal reasons not disclosed	I	No	N/A

Table 21. Study Adverse Events, Fed Bioequivalence Study

Body System* / Adverse Event	Reported Incidence by Treatment Groups (%)	
	Fed Bioequivalence Study (Study No.: ILOP-1K-570-13/ LBC-13-081)	
	TEST	REFERENCE
Cardiac disorders / Giddiness	9.68 % (03)	10.00 % (03)
Gastro intestinal disorders / Nausea	N/A	3.33 % (01)
Nervous system disorders/ Somnolence	N/A	10.00 % (03)
Total	9.68 % (03)	23.33 % (07)

*Per the RLD labeling, the commonly observed adverse reactions (incidence $\geq 5\%$ and 2-fold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increased. All the observed adverse events are included in the RLD labeling.⁶

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
None				

Was the adverse event profile observed during the fed bioequivalence study comparable for the test and reference product? Please comment.

Yes

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee?

None

Are there any other safety concerns based on the adverse event profile?

None

⁶ DRUGS@FAD, search term: Fanapt, last accessed on May, 2015.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022192s013lbl.pdf

Table 22. Protocol Deviations, Fed Bioequivalence Study

(Study No. ILOP-1K-570-13/ LBC-13-081)			
S. No.	Type	Subject ID (Test)	Subject ID (Reference)
01	As per section (s) 15.2 and 15.3 of the protocol, post study assessments (ECG and laboratory assessments) could not be performed for Subject nos. S07 and S16. Because, Subject no. (b) (6) was withdrawn from the study before dosing of Period II, due to “failed to comply with restrictions and prohibitions” and (b) (6) did not report to facility for Period II check-in. Subjects were communicated through phone and informed to visit to the facility for post study sample collection. But, both were not visited to the facility due to personal reasons. However, the well-being & safety of these subjects was confirmed over telephonic calls to each. It has been concluded to have no impact on the overall outcome of the study.	Not applicable	Not applicable

Comments:

1. A total of 34 subjects were enrolled in the study. Twenty-nine (29) out of 32 dosed subjects completed the study. Subject no. (b) (6) dropped out of the study due to failure in complying with restrictions and prohibitions in Period-II. Subject no (b) (6) dropped out of the study due to failed to report to the facility for Period II check-in. Subject no (b) (6) withdraw from the study due to personal reasons in Period-I. The reviewer verified the dropout of the subjects from the case report forms (CRFs).
2. A total of ten adverse events were reported in the study, all of which were found to be mild in intensity but considered as related to the administration of study products. Of the ten adverse events, three were reported after administration of the test product and seven were reported after administration of the reference product. All the adverse events were resolved on the same day without any sequelae. There was no vomiting reported in this study. There were no serious adverse events or deaths reported in the study. There were no concomitant medications administered for any of the adverse events in this study. The reviewer verified the adverse events from the case report forms (CRFs).
3. There were 2 protocol deviations. As per protocol, ECG was recorded at the time of check-out (ECG) of Period II. Post study assessments (ECG and laboratory assessments) could not be performed for Subject nos (b) (6) because Subject no. (b) (6) was withdrawn from the study before dosing of Period II due to failed to comply with restrictions and prohibitions and Subject no. (b) (6) did not report to facility for Period II check-in. Subjects were communicated through phone and

informed to visit the facility for post study sample collection. But, both were not visited to the facility due to personal reasons. However, the well-being & safety of these subjects was confirmed over telephonic calls to each. The reviewer considers that the protocol deviations had no impact on the overall outcome of the study since the subjects didn't complete the study and was not included in the data analysis.

APPEARS THIS WAY ON
ORIGINAL

4.1.2.3 Bioanalytical Results

Table 23. Sample Analysis Calibration and Quality Control

Bioequivalence Study Code: LBC-13-081 Fed Study Analyte: Iloperidone								
Parameter	Standard Curve Samples							
	CS 8	CS 7	CS 6	CS 5	CS 4	CS 3	CS 2	CS 1
Concentration (pg/ml)	10046.32 8	8237.98 9	6178.49 2	4121.05 4	2060.52 7	1030.26 4	201.41 7	100.70 8
Inter day Precision (% CV)	4.66	4.34	5.47	4.67	8.00	5.25	13.13	3.05
Inter day Accuracy (% Actual)	100.84	99.88	100.49	98.12	101.40	102.45	99.45	100.44
Linearity (r)	0.994940-0.999542							
Linearity Range (pg/ml)	100.708-10046.328							
Sensitivity/LLO Q (pg/ml)	100.708							

Bioequivalence Study Code: LBC-13-081 Fed Study Analyte: Iloperidone				
Parameter	Quality Control Samples			
	HQC	MQC	MIQC	LQC
Concentration (pg/ml)	7120.796	4130.062	2011.524	276.714
Inter day Precision (%CV)	5.56	5.27	3.89	11.49
Inter day Accuracy (%Actual)	98.14	98.89	101.53	97.40

Bioequivalence Study Code: LBC-13-081 Fed Study Analyte: Iloperidone P88								
Parameter	Standard Curve Samples							
	CS 8	CS 7	CS 6	CS 5	CS 4	CS 3	CS 2	CS 1
Concentration (pg/ml)	10015.92 2	8213.05 6	6159.79 2	4108.58 1	2054.29 1	1027.14 5	200.80 7	100.40 3
Inter day Precision (% CV)	5.57	4.56	5.15	3.73	5.93	5.86	5.41	2.77
Inter day Accuracy (% Actual)	101.64	99.57	99.36	97.99	99.96	101.35	100.44	99.70
Linearity (r)	0.995418-0.999347							
Linearity Range (pg/ml)	100.403-10015.922							
Sensitivity/LLO Q (pg/ml)	100.403							

Bioequivalence Study Code: LBC-13-081 Fed Study

Analyte: Iloperidone P88				
Parameter	Quality Control Samples			
	HQC	MQC	M1QC	LQC
Concentration (pg/ml)	7099.638	4117.790	2005.547	275.892
Inter day Precision (%CV)	10.66	7.63	6.10	10.66
Inter day Accuracy (%Actual)	99.02	97.41	102.28	97.19

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Are there any concerns related to sample reanalysis or run rejection?	No

Were 20% of chromatograms included?	Yes (subjects (b) (6))
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log) in the instrument printout format?	Yes

Table 24. SOP's Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
AAP-13-014-00	04/15/2013	Estimation of Iloperidone and Iloperidone P88 in Human Plasma using UPLC-MS/MS
LBC-BR024-05	07/16/2012	Repeat Sample Analysis
LBC-BR023-03	09/11/2012	Study Sample Analysis and Analytical Run Acceptance Criteria
LBC-BR025-02	11/21/2011	Incurred Sample Reanalysis
LBC-BR014-02	11/02/2012	Assessment of Quality of Chromatogram

Comments:

For ISR, 104 (11.22% of 927 samples) were analysed as part of the incurred sample reanalysis (100 samples both Iloperidone and Iloperidone P88, 02 samples for Iloperidone only, and 02 samples for Iloperidone P88 only). The variability of 85.87% and 95.74% of reanalyzed samples are acceptable for Iloperidone and Iloperidone P88, respectively as shown in the tables below. Per acceptance criteria in the SOP # LBC-BR025-02 that the percentage difference of the original and repeat values must be within $\pm 20\%$. And 75% of the total incurred samples analyzed (irrespective of the number of analytical batches) must meet the criteria. Therefore, the assay is considered reproducible.

• **Summary of Incurred sample Reanalysis for Iloperidone**

No. of samples analysed	102
No. of samples rejected due to analytical reason	10 (IS variation)

ANDA 206890
Single-Dose Fed Bioequivalence Study Review

No. of valid ISR samples	92
No. of failed ISR samples	13
No. of passed ISR samples	79
Percentage of the within acceptance criteria (%)	85.87%

- **Summary of Incurred sample Reanalysis for Iloperidone P88**

No. of samples analysed	102
No. of samples rejected due to analytical reason	08(IS variation)
No. of valid ISR samples	94
No. of failed ISR samples	04
No. of passed ISR samples	90
Percentage of the within acceptance criteria (%)	95.74%

4.1.2.4 Pharmacokinetic Results

Table 25. Mean Pharmacokinetic Parameters (Firm calculated)

Iloperidone Firm Calculated																
PK parameter (Units)	N	Mean		SD		Min		Median		Max		CV%		Geometric Mean		Ratio
		T	R	T	R	T	R	T	R	T	R	T	R	T	R	
T _{max} (hr)	29	3.379	3.241	1.545	1.185	2.00	1.00	3.00	3.00	10.00	6.00	45.72	36.55	3.157	3.010	100
C _{max} (pg/mL)	29	3019.9901	3034.1579	1211.6461	1077.0255	833.7177	1109.007	3037.577	2741.814	6321.373	6383.556	40.12	35.50	2784.3318	2858.9071	99.53306
AUC _{0-t} (pg*hr/mL)	29	56156.6772	56129.8499	25654.0394	29168.7686	31572.358	26433.783	52701.801	48606.982	163370.886	176052.305	45.68	51.97	52340.8240	51302.9158	100.0478
AUC _{0-∞} (pg*hr/mL)	29	63760.5992	63543.8820	28526.2591	31562.1575	37163.970	35041.075	58064.913	52954.840	183060.866	193268.845	44.74	49.67	59642.8312	58604.3517	100.3411
K _{el} (hr ⁻¹)	29	0.0279	0.0269	0.0101	0.0084	0.014	0.015	0.026	0.025	0.057	0.049	36.18	31.14	0.0263	0.0257	103.7175
t _{1/2} (hr)	29	27.935	28.097	9.417	8.085	12.22	14.09	26.90	28.15	48.41	46.46	33.71	28.77	26.401	26.960	99.42343
AUC _{%Extrap_{obs}} (%)	29	12.0996	12.2822	5.0410	5.4923	5.380	6.740	10.756	10.578	24.002	27.021	41.66	44.72	11.1322	11.3499	98.5133

Iloperidone P88 Firm Calculated																
PK parameter (Units)	N	Mean		SD		Min		Median		Max		CV%		Geometric Mean		Ratio
		T	R	T	R	T	R	T	R	T	R	T	R	T	R	
T _{max} (hr)	29	5.414	4.862	1.900	1.684	2.00	2.00	5.00	5.00	10.00	8.00	35.09	34.65	5.103	4.556	100
C _{max} (pg/mL)	29	3261.6138	3320.2413	942.5238	977.6737	430.255	687.369	3251.732	3194.605	5823.676	5423.004	28.90	29.45	3060.9224	3141.1932	98.23424
AUC _{0-t} (pg*hr/mL)	29	91403.9117	90074.5516	23089.5739	23800.1688	7994.551	13184.426	90738.933	90440.333	126742.669	142184.025	25.26	26.42	85394.9737	85132.6820	101.4758
AUC _{0-∞} (pg*hr/mL)	29	101153.2150	99768.2276	26565.7709	25776.0060	11756.161	19971.743	101799.023	98487.436	149822.880	160230.929	26.26	25.84	95032.7610	95136.4109	101.3882
K _{el} (hr ⁻¹)	29	0.0262	0.0241	0.0061	0.0049	0.017	0.012	0.025	0.024	0.040	0.033	23.21	20.40	0.0255	0.0235	108.7137
t _{1/2} (hr)	29	27.867	30.218	6.387	7.540	17.39	21.06	27.63	28.80	41.18	57.01	22.92	24.95	27.168	29.458	92.21987
AUC _{%Extrap_{obs}} (%)	29	9.9743	10.3239	5.2731	5.5812	3.220	3.935	9.326	9.393	31.997	33.985	52.87	54.06	9.0387	9.3682	96.61368

Table 26. Summary of Geometric Least Square Mean, Ratios and 90% Confidence

ANDA 206890
Single-Dose Fed Bioequivalence Study Review

Iloperidone

Parameter	N		Geometric Least Square Means		Ratio T/R (%)	90% CI	p-value		
	T	R	T	R			Formulation	Period	Sequence
C _{max} (pg/mL)	29	29	2783.0641	2863.0469	97.21	91.07 to 103.76	0.4660	0.1614	0.8417
AUC _{0-t} (pg*hr/mL)	29	29	52342.3821	51427.5583	101.78	97.34 to 106.42	0.5066	0.0132	0.6162
AUC _{0-∞} (pg*hr/mL)	29	29	59678.6629	58772.7872	101.54	97.74 to 105.49	0.5010	0.0067	0.4575
Parameter	ISCV (%)		Power		T- Test Product – Iloperidone Tablets 1 mg of Lupin limited, India. R - Reference Product– Fanapt® (Iloperidone) Tablets 1 mg Manufactured by (b) (4) N-Number of Observations				
C _{max}	14.58		0.9998						
AUC _{0-t}	9.97		1.0000						
AUC _{0-∞}	8.53		1.0000						

active P88 metabolite

Parameter	N		Geometric Least Square Means		Ratio T/R (%)	90% CI	p-value		
	T	R	T	R			Formulation	Period	Sequence
C _{max} (pg/mL)	29	29	3045.7058	3129.2174	97.33	92.54 to 102.37	0.3697	0.2650	0.0853
AUC _{0-t} (pg*hr/mL)	29	29	85098.4020	84907.0535	100.23	96.45 to 104.15	0.9212	0.2982	0.2924
AUC _{0-∞} (pg*hr/mL)	29	29	94787.1171	94972.7130	99.80	96.01 to 103.74	0.9321	0.2792	0.4116
Parameter	ISCV (%)		Power		T- Test Product – Iloperidone Tablets 1 mg of Lupin limited, India. R - Reference Product– Fanapt® (Iloperidone) Tablets 1 mg Manufactured by (b) (4) N-Number of Observations				
C _{max}	11.28		1.0000						
AUC _{0-t}	8.58		1.0000						
AUC _{0-∞}	8.66		1.0000						

Is there a Tmax difference between T and R	No. The median Tmax is 3.00 hrs for both the T and R for Iloperidone. The median Tmax is 5.00 hrs for both the T and R for Iloperidone P88.
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Sampling time is adequate. The AUC _{0-t} /AUC _{0-∞} ratios of all but 6 subjects are > 80.00% for Iloperidone.

Reviewer's note: A total of 6 subjects (three for the test product, three for the reference product) had AUC_{0-t}/AUC_{0-∞} ratios below 80.00% in terms of Iloperidone but the differences are small as shown in the table below. The reviewer also checked the semi-log plasma concentration time profiles for these subjects and the sampling schedule has adequately captured the elimination phase for all these subjects. The average AUC₀₋

$t/AUC_{0-\infty}$ ratios of T and R are 87.90% and 87.72%, respectively. Therefore, the reviewer considers that the sampling time is adequate.

Subject	Treatment	Period	AUC_{0-t}/AUC_{∞} ratio
(b) (6)	R	I	75.44
	R	I	78.41
	R	II	72.98
	T	I	76.00
	T	II	78.92
	T	I	79.13

Overall Comment:

1. As per the current DB policy, the firm's statistical analyses were evaluated by the reviewer. Based on the firm's calculation, the 90% confidence intervals for $\ln AUC_{0-t}$, $\ln AUC_{0-\infty}$ and $\ln C_{\max}$ of iloperidone are within the BE acceptance limits of 80.00-125.00%.
2. The pharmacokinetic (PK) parameters of the test and reference products for the active metabolite P88 are comparable. Therefore, the iloperidone P88 data are supportive.
3. Per the RLD labeling, administration of iloperidone with a standard high-fat meal did not significantly affect the $C_{\max}$ or AUC of iloperidone, P88, or P95, but delayed $T_{\max}$ by 1 hour for iloperidone, 2 hours for P88 and 6 hours for P95. FANAPT can be administered without regard to meals. The food effect indicated by the PK results of the current fed study is consistent with the RLD labeling.
4. The fed *in vivo* bioequivalence study is adequate.

**Table 27. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study
(Firm-submitted Data in Firm's Format)**

Mean plasma Iloperidone Concentrations (pg /mL) for Test Product

Time (hr)	N	Mean (pg /mL)	SD (pg /mL)	Min (pg /mL)	Max (pg /mL)	CV%
0.00	29	0.0000	0.0000	0.000	0.000	0.00
1.00	29	830.0451	1043.6254	0.000	4325.703	125.73
2.00	29	2097.0462	1386.3572	272.189	6321.373	66.11
3.00	29	2611.7859	1025.5131	695.139	4783.052	39.26
4.00	29	2390.2683	841.1078	833.717	3875.333	35.19
5.00	29	1895.8803	869.8038	718.467	4428.512	45.88
6.00	29	2016.9466	913.0633	692.010	4449.692	45.27
8.00	29	1773.5776	786.3072	743.065	4570.776	44.33
10.00	29	1418.2546	896.5824	488.755	4984.598	63.22
12.00	29	1367.4781	627.3833	671.656	3939.086	45.88
16.00	29	1035.3903	533.7703	488.487	3335.447	51.55
24.00	29	736.1773	417.4314	326.603	2642.461	56.70
36.00	29	541.1154	261.1198	295.796	1650.393	48.26
48.00	29	386.0863	222.4997	143.003	1377.084	57.63
72.00	29	215.8818	134.1431	0.000	710.683	62.14
96.00	29	118.3097	114.3600	0.000	492.104	96.66

Mean plasma Iloperidone Concentrations (pg /mL) for Reference Product

Time (hr)	N	Mean (pg /mL)	SD (pg /mL)	Min (pg /mL)	Max (pg /mL)	CV%
0.00	28	6.1551	32.5700	0.000	172.344	529.15
1.00	29	1053.9669	1124.4269	0.000	3949.188	106.69
2.00	29	2175.5679	981.6458	696.178	4558.258	45.12
3.00	29	2679.1181	1152.8621	694.278	6345.348	43.03
4.00	29	2503.4348	1036.8134	722.151	6383.556	41.42
5.00	29	1935.1497	963.4064	707.118	5647.409	49.78
6.00	29	2057.2918	874.5282	902.198	5160.728	42.51
8.00	29	1786.2030	832.1435	847.903	4884.596	46.59
10.00	29	1338.8206	902.0120	515.441	5060.679	67.37
12.00	29	1329.5213	699.0341	581.951	4273.058	52.58
16.00	29	1044.3378	569.2061	488.055	3332.138	54.50
24.00	29	730.2885	477.2843	335.449	2872.426	65.36
36.00	28	540.9544	328.6929	188.986	1861.190	60.76
48.00	29	378.0518	200.1630	187.096	1177.552	52.95
72.00	29	204.8563	136.7535	0.000	682.668	66.76
96.00	29	122.4849	110.7964	0.000	488.360	90.46

Mean plasma Iloperidone P88 Concentrations (pg /mL) for Test Product

Time (hr)	N	Mean (pg /mL)	SD (pg /mL)	Min (pg /mL)	Max (pg /mL)	CV%
0.00	28	0.0000	0.0000	0.000	0.000	0.00
1.00	29	583.5177	568.3902	0.000	2376.841	97.41
2.00	29	1824.8067	937.5985	0.000	3535.996	51.38
3.00	29	2551.6283	1066.5627	0.000	5427.973	41.80
4.00	29	2828.3546	1012.2805	272.756	5823.676	35.79
5.00	29	3083.6144	881.1677	331.761	5209.054	28.58
6.00	29	2944.2555	794.3448	430.255	4658.193	26.98
8.00	29	2764.5617	685.7969	380.971	3855.258	24.81
10.00	29	2534.1918	599.4687	221.480	3309.303	23.66
12.00	29	2253.9412	550.7516	366.257	3075.235	24.44
16.00	29	1776.0466	454.9839	281.465	2753.620	25.62
24.00	29	1488.2409	377.6258	188.979	2039.349	25.37
36.00	29	867.3360	247.1456	143.733	1267.670	28.49
48.00	29	648.4675	201.4247	0.000	1022.323	31.06
72.00	29	350.6124	143.9669	0.000	688.721	41.06
96.00	29	226.7969	87.1846	0.000	407.454	38.44

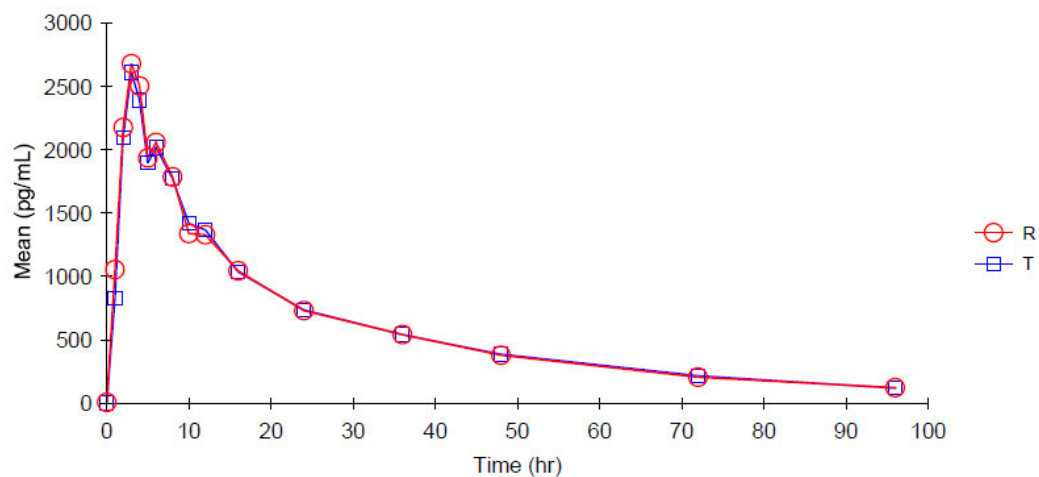
Mean plasma Iloperidone P88 Concentrations (pg /mL) for Reference Product

Time (hr)	N	Mean (pg /mL)	SD (pg /mL)	Min (pg /mL)	Max (pg /mL)	CV%
0.00	27	5.5944	29.0696	0.000	151.050	519.62
1.00	29	984.4402	1087.5136	0.000	4181.651	110.47
2.00	29	2089.8667	1251.8034	0.000	5423.004	59.90
3.00	29	2657.5746	1155.5203	239.629	5392.921	43.48
4.00	29	2885.7620	1009.3554	438.125	5315.928	34.98
5.00	29	3102.9405	849.8768	598.136	4611.349	27.39
6.00	29	2962.3940	802.3504	687.369	4507.126	27.08
8.00	29	2720.8100	670.0769	463.498	4013.795	24.63
10.00	29	2569.0679	632.1475	416.076	3397.928	24.61
12.00	29	2153.1649	570.2353	349.158	3027.493	26.48
16.00	29	1724.2298	430.3847	276.296	2502.938	24.96
24.00	29	1461.0435	390.5669	211.598	2456.932	26.73
36.00	28	859.9440	264.8960	0.000	1534.583	30.80
48.00	29	610.9240	207.3101	167.602	1146.876	33.93
72.00	29	333.6851	117.4707	106.689	657.684	35.20
96.00	29	219.9548	88.5814	0.000	402.752	40.27

**Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study
(Firm-submitted Plot)**

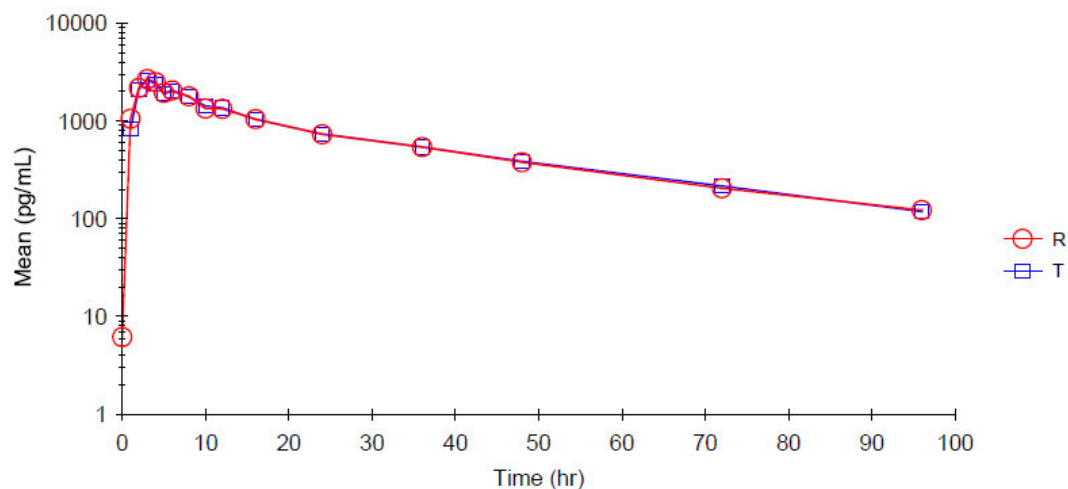
Linear plot of mean plasma concentrations versus time of Iloperidone for Test product (T) and Reference product ® in 29 healthy, adult, human male subjects under fed conditions

LBC-13-081
Iloperidone



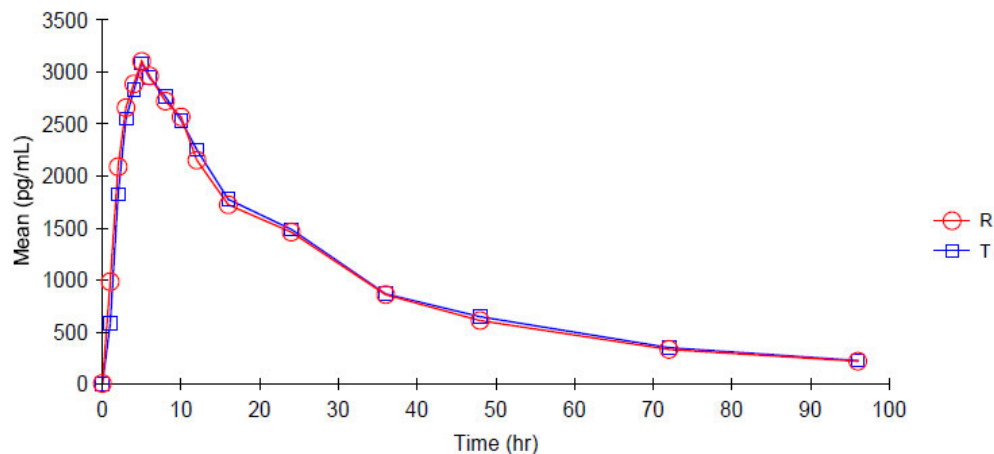
Semi log plot of mean plasma concentrations versus time of Iloperidone for Test product (T) and Reference product ® in 29 healthy, adult, human male subjects under fed conditions

LBC-13-081
Iloperidone



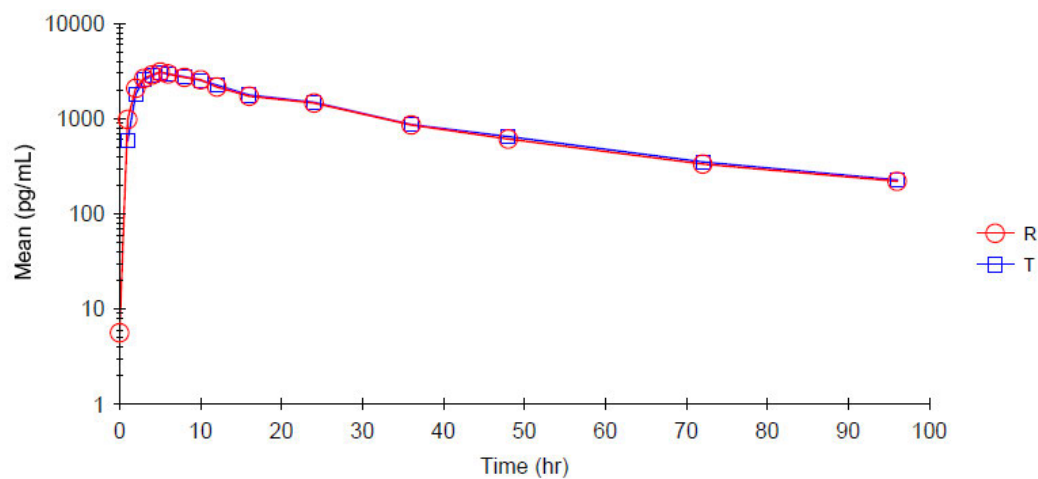
Linear plot of mean plasma concentrations versus time of Iloperidone P88 for Test product (T) and Reference product ® in 29 healthy, adult, human male subjects under fed conditions

LBC-13-081
active P88 metabolite



Semi log plot of mean plasma concentrations versus time of Iloperidone P88 for Test product (T) and Reference product ® in 29 healthy, adult, human male subjects under fed conditions

LBC-13-081
active P88 metabolite



2 Pages have been withheld in full as b4
CCI/TS immediately following this page

(b) (4)

Reviewer's note

The formulation of 2 mg strength of Iloperidone Tablets is proportionally similar to that of 1 mg strength (b) (4)

The formulations of Iloperidone Tablets of 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets are also considered proportionally similar to that of the bio-strength, 1mg as per the limit (b) (4) allowed for

(b) (4)

(b) (4)

(b) (4)						
---------	--	--	--	--	--	--

*As per the RLD label, the Maximum Daily Dose (MDD) is 24 mg. All the amounts of inactive ingredients are based on MDD of 24 mg/day of the active ingredient.



(b) (4)

***The total amount of the Sodium Starch Glycolate is still below the IIG limit of 876.0 mg.

(b) (4)



(b) (4)

Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD)	NO
---	----



(b) (4)

⁸ DailyMed; <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3495a70c-870c-4968-940e-8baea152cf85>

within IIG (per unit) limits?	
If no, are they all above/within IIG (per day) limits?	YES
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	N/A
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	YES

Overall Comment:

The formulations of all 7 strengths are acceptable.

The formulations of the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths of the test product are proportionally similar to that of the bio-strength, 1 mg.

4.3 Dissolution Data (Applicable if there are waiver requests)

Dissolution Review Path	Panorama: ANDA 206890: Biopharmaceutical Quality Review, by Katherine Szeszypalow, 02/25/2015 and Tiffany Pokora, 04/10/2015
--------------------------------	--

Table 28. Dissolution Data

Dissolution Conditions		Apparatus:		USP Type II (Paddle)								
		Speed of Rotation:		50 rpm								
		Medium:		0.1 N Hydrochloric Acid (b) (4)								
		Volume:		500 mL								
		Temperature:		37 °C ± 0.5°C								
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes										
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location
						5	10	15	30	45	60	
STP-1226-01	February 15, 2013	Iloperidone Tablets, 1 mg [Batch No.: G390057*] [Lupin Limited] Manufacturing Date: January 2013	1 mg, Tablets	12	Mean	81	90	93	96	96	96	(b) (4)
					Range							
					%CV	7.89	4.52	4.29	2.83	2.28	2.51	
STP-1226-01	February 14, 2013	FANAPT® (iloperidone) Tablets, 1 mg [Batch No.: FFZN] (b) (4) Expiry Date: April 2015	1 mg, Tablets	12	Mean	94	96	96	97	97	97	(b) (4)
					Range							
					%CV	3.10	3.53	4.44	3.66	3.01	3.29	

m5.3.1.3

* Batch number G390074 is for 60's HDPE Bottle pack used in the bioequivalence (BE) studies and accordingly reflected in all BE study and related documents. It is noted that the parent batch is G390057.

Dissolution Conditions	Apparatus:	USP Type II (Paddle)				
	Speed of Rotation:	50 rpm				

		Medium:	0.1 N Hydrochloric Acid (b) (4)									
		Volume:	500 mL									
		Temperature:	37 °C ± 0.5°C									
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes										
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location
						5	10	15	30	45	60	
STP-1227-01	February 16, 2013	Iloperidone Tablets, 2 mg [Batch No.: G390058] [Lupin Limited] Manufacturing Date: January 2013	2 mg, Tablets	12	Mean	79	88	92	94	98	97	m5.3.1.3
					Range	(b) (4)						
					%CV	6.27	5.35	5.21	5.16	4.65	4.67	
STP-1227-01	March 21, 2013	FANAPT® (iloperidone) Tablets, 2 mg [Batch No.: HKSY1 (b) (4)] Expiry Date: March 2015	2 mg, Tablets	12	Mean	81	90	93	96	96	97	
					Range	(b) (4)						
					%CV	6.60	4.80	3.17	2.36	1.44	2.03	

Dissolution Conditions	Apparatus:	USP Type II (Paddle)		
	Speed of Rotation:	50 rpm		
	Medium:	0.1 N Hydrochloric Acid	(b) (4)	
	Volume:	500 mL		
	Temperature:	37 °C ± 0.5°C		
Firm's Proposed Specifications	Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes			
Dissolution Testing Site (Name, Address)	Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.			

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1228-01	February 22, 2013	Iloperidone Tablets, 4 mg [Batch No.: G390061] [Lupin Limited] Manufacturing Date: January 2013	4 mg, Tablets	12	Mean	74	85	89	92	93	92	m5.3.1.3	
					Range	(b) (4)							
					%CV	7.44	5.51	4.69	3.64	3.62	3.23		
STP-1228-01	March 23, 2012	FANAPT® (iloperidone) Tablets, 4 mg [Batch No.: HKTb] (b) (4) Expiry Date: May 2015	4 mg, Tablets	12	Mean	86	92	95	96	97	(b) (4)		
					Range								
					%CV	7.73	3.51	3.77	2.15	1.67			1.61

Dissolution Conditions		Apparatus:	USP Type II (Paddle)									
		Speed of Rotation:	50 rpm									
		Medium:	0.1 N Hydrochloric Acid (b) (4)									
		Volume:	500 mL									
		Temperature:	37 °C ± 0.5°C									
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes										
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location
						5	10	15	30	45	60	
STP-1229-01	February 18, 2013	Iloperidone Tablets, 6 mg [Batch No.: G390062] [Lupin Limited] Manufacturing Date: January 2013	6 mg, Tablets	12	Mean	77	89	95	99	101	102	m5.3.1.3
					Range	(b) (4)						
					%CV	7.37	4.89	2.94	3.01	2.65	3.63	
STP-1229-01	March 26, 2013	FANAPT® (iloperidone) Tablets, 6 mg [Batch No.: GVSK] (b) (4) Expiry Date: January 2015	6 mg, Tablets	12	Mean	80	94	96	97	97		
					Range	(b) (4)						
					%CV	12.87	3.90	2.75	1.23	1.06	1.15	

Dissolution Conditions		Apparatus:		USP Type II (Paddle)								
		Speed of Rotation:		50 rpm								
		Medium:		0.1 N Hydrochloric Acid (b) (4)								
		Volume:		500 mL								
		Temperature:		37 °C ± 0.5°C								
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes										
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location
						5	10	15	30	45	60	
STP-1230-01	February 19, 2013	Iloperidone Tablets, 8 mg [Batch No.: G390063] [Lupin Limited] Manufacturing Date: January 2013	8 mg, Tablets	12	Mean	71	85	90	93	94	94	m5.3.1.3
					Range	(b) (4)						
					%CV	7.54	4.29	2.66	1.68	1.56	1.54	
STP-1230-01	April 1, 2013	FANAPT® (iloperidone) Tablets, 8 mg [Batch No.: HPEFG] (b) (4) Expiry Date: April 2015	8 mg, Tablets	12	Mean	83	89	88	96	99	100 (b) (4)	
					Range	(b) (4)						
					%CV	7.68	6.58	7.02	3.42	3.12	3.26	

Dissolution Conditions		Apparatus:	USP Type II (Paddle)									
		Speed of Rotation:	50 rpm									
		Medium:	0.1 N Hydrochloric Acid (b) (4)									
		Volume:	500 mL									
		Temperature:	37 °C ± 0.5°C									
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes										
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location
						5	10	15	30	45	60	

STP-1231-01	February 20, 2013	Iloperidone Tablets, 10 mg [Batch No.: G390064] [Lupin Limited] Manufacturing Date: January 2013	10 mg, Tablets	12	Mean	69	82	87	91	91	91	(b) (4)	
					Range								
					%CV	7.27	5.25	3.92	3.82	3.14	2.75		
STP-1231-01	March 25, 2013	FANAPT® (iloperidone) Tablets, 10 mg [Batch No.: HBXW] (b) (4)	10 mg, Tablets	12	Mean	70	80	87	92	95	96	(b) (4)	
					Range								
					%CV	15.06	10.03	7.14	4.35	2.63	1.98		

m5.3.1.3

[m5.3.1.3](#)

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1232-01	February 21, 2013	Iloperidone Tablets, 12 mg [Batch No.: G390065] [Lupin Limited] Manufacturing Date: January 2013	12 mg, Tablets	12	Mean	71	85	91	94	94	95	(b) (4)	
					Range								
					%CV	3.60	2.89	3.71	2.10	2.37	2.40		
STP-1232-01	March 7, 2013	FANAPT® (iloperidone) Tablets, 12 mg [Batch No.: HBHD] (b) (4)	12 mg, Tablets	12	Mean	63	73	79	90	94	97	(b) (4)	
					Range								
					%CV	19.98	16.41	12.96	6.32	3.71	1.99		

[m5.3.1.3](#)

Comparison to 1 mg strength

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1227-01	February 16, 2013	Iloperidone Tablets, 2 mg [Batch No.: G390058] [Lupin Limited] Manufacturing Date: January 2013	2 mg, Tablets	12	Mean	79	88	92	94	98	97	m5.3.1.3	
					Range	(b) (4)							
					%CV	6.27	5.35	5.21	5.16	4.65	4.67		
STP-1226-01	February 15, 2013	Iloperidone Tablets, 1 mg [Batch No.: G390057] [Lupin Limited] Manufacturing Date: January 2013	1 mg, Tablets	12	Mean	81	90	93	96	96	96		
					Range	(b) (4)							
					%CV	7.89	4.52	4.29	2.83	2.28	2.51		

Dissolution Conditions		Apparatus:		USP Type II (Paddle)								
		Speed of Rotation:		50 rpm								
		Medium:		0.1 N Hydrochloric Acid						(b) (4)		
		Volume:		500 mL								
		Temperature:		37 °C ± 0.5°C								
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes										
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date)	Dosage Strength	No. of Dosage		Collection Times (minutes)						Study Report
						5	10	15	30	45	60	

		(Reference – Expiration Date)	& Form	Units								Location
STP-1228-01	February 22, 2013	Iloperidone Tablets, 4 mg [Batch No.: G390061] [Lupin Limited] Manufacturing Date: January 2013	4 mg, Tablets	12	Mean	74	85	89	92	93	92	m5.3.1.3
					Range	(b) (4)						
					%CV	7.44	5.51	4.69	3.64	3.62	3.23	
STP-1226-01	February 15, 2013	Iloperidone Tablets, 1 mg [Batch No.: G390057] [Lupin Limited] Manufacturing Date: January 2013	1 mg, Tablets	12	Mean	81	90	93	96	96	96	
					Range	(b) (4)						
					%CV	7.89	4.52	4.29	2.83	2.28	2.51	

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1229-01	February 18, 2013	Iloperidone Tablets, 6 mg [Batch No.: G390062] [Lupin Limited] Manufacturing Date: January 2013	6 mg, Tablets	12	Mean	77	89	95	99	101	102	m5.3.1.3	
					Range	(b) (4)							
					%CV	7.37	4.89	2.94	3.01	2.65	3.63		
STP-1226-01	February 15, 2013	Iloperidone Tablets, 1 mg [Batch No.: G390057] [Lupin Limited] Manufacturing Date: January 2013	1 mg, Tablets	12	Mean	81	90	93	96	96	(b) (4)		
					Range	(b) (4)							
					%CV	7.89	4.52	4.29	2.83	2.28			2.51

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1230-01	February 19, 2013	Iloperidone Tablets, 8 mg [Batch No.: G390063] [Lupin Limited] Manufacturing Date: January 2013	8 mg, Tablets	12	Mean	71	85	90	93	94	94	m5.3.1.3	
					Range	(b) (4)							
					%CV	7.54	4.29	2.66	1.68	1.56	1.54		
STP-1226-01	February 15, 2013	Iloperidone Tablets, 1 mg [Batch No.: G390057] [Lupin Limited] Manufacturing Date: January 2013	1 mg, Tablets	12	Mean	81	90	93	96	96	96		
					Range	(b) (4)							
					%CV	7.89	4.52	4.29	2.83	2.28	2.51		

Dissolution Conditions		Apparatus:	USP Type II (Paddle)									
		Speed of Rotation:	50 rpm									
		Medium:	0.1 N Hydrochloric Acid (b) (4)									
		Volume:	500 mL									
		Temperature:	37 °C ± 0.5°C									
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes										
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location
						5	10	15	30	45	60	

STP-1231-01	February 20, 2013	Iloperidone Tablets, 10 mg [Batch No.: G390064] [Lupin Limited] Manufacturing Date: January 2013	10 mg, Tablets	12	Mean	69	82	87	91	91	91	m5.3.1.3	
					Range	(b) (4)							
					%CV	7.27	5.25	3.92	3.82	3.14	2.75		
STP-1226-01	February 15, 2013	Iloperidone Tablets, 1 mg [Batch No.: G390057] [Lupin Limited] Manufacturing Date: January 2013	1 mg, Tablets	12	Mean	81	90	93	96	96	96		
					Range	(b) (4)							
					%CV	7.89	4.52	4.29	2.83	2.28	2.51		

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1232-01	February 21, 2013	Iloperidone Tablets, 12 mg [Batch No.: G390065] [Lupin Limited] Manufacturing Date: January 2013	12 mg, Tablets	12	Mean	71	85	91	94	94	95	m5.3.1.3	
					Range	(b) (4)							
					%CV	3.60	2.89	3.71	2.10	2.37	2.40		
STP-1226-01	February 15, 2013	Iloperidone Tablets, 1 mg [Batch No.: G390057] [Lupin Limited] Manufacturing Date: January 2013	1 mg, Tablets	12	Mean	81	90	93	96	96	96		
					Range	(b) (4)							
					%CV	7.89	4.52	4.29	2.83	2.28	2.51		

Please comment on whether dissolution data are adequate to support waiver requests.	Adequate
---	----------

--	--

Overall Comment:

1. The dissolution data for quality control and stability purpose have been previously reviewed⁹. According to the dissolution-only review, the firm has conducted acceptable comparative dissolution testing on all 7 strengths of the Iloperidone Tablets using the FDA recommended dissolution method [500 mL of 0.1 N Hydrochloric Acid, Apparatus II (Paddle) at 50 rpm].
2. Since (b) (4) % of drug release has been achieved at 15 minute time point for the test product for all 7 strengths (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg), the calculation of f2 values are not necessary for comparison of the dissolution profiles of the test products. All 7 strengths of the test products are rapidly dissolved in the dissolution medium. The dissolution profiles of 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths of the test product are considered comparable.
3. The dissolution data are adequate with respect to supporting waiver request of the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths.

⁹ Panorama: ANDA 206890: Biopharmaceutical Quality Review, by Katherine Szeszypalow, 02/25/2015 and Tiffany Pokora, 04/10/2015
<http://panorama.fda.gov/task/view?ID=5421498b005b8e1a00d0e0717a066237>

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 206890

APPLICANT: Lupin Limited

DRUG PRODUCT: Iloperidone Tablets: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Wayne I. DeHaven, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	206890
Drug Product Name	Iloperidone Tablets
Strength (s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12mg
Applicant Name	Lupin Limited
Applicant Address	159, CST Road Kalina, Santacruz (East) Mumbai, India 400098
US Agent Name and the mailing address	Ms. Leslie Sands - Director, Regulatory Affairs Lupin Pharmaceuticals, Inc., III South Calvert Street Harborplace Tower, 21st Floor Baltimore, Maryland 21202
US Agent's Telephone Number	(410) 576-2000
US Agent's Fax Number	(410) 576-2221
Original Submission Date(s)	05/08/2014
Submission Date(s) of Amendment(s) Under Review	-
Reviewer	Katherine Szeszypalow
Dissolution Method	ADEQUATE
OVERALL REVIEW RESULT	INADEQUATE

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

This application references Fanapt® (iloperidone) tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths (NDA # 022192, approved on May 6, 2009 and manufactured by (b) (4)).

There is no USP method for this product but there is an FDA- recommended method. [500mL of 0.1 N HCl using USP apparatus II (paddle) @ 50 rpm]. The firm's dissolution testing data with the FDA-recommended are acceptable.

The firm's proposed specification [NLT (b) (4)% (Q) in (b) (4) minutes] is too broad and not supported by their data and therefore not acceptable. The Division of Bioequivalence (DB) recommends a more stringent specification: NLT (b) (4)% (Q) in 30 minutes. The firm provided data of the test product meet the DB recommended specification. The firm should acknowledge the FDA-recommended method and specification.

The in vitro dissolution testing is incomplete.

II. DISSOLUTION REVIEW

II.1 Submission Content Checklist

Information	YES	NO	N/A
Is there a posted dissolution method on the FDA website?	☒	☐	☐
Did the firm use the above method?	☒	☐	☐
Is there a USP dissolution method?	☐	☒	☐
Did the firm use the USP dissolution method?	☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing?	☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)?	☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method?	☐	☒	☐
Did the firm submit dissolution method validation?	☒	☐	☐

II.2 Dissolution Method As Posted on the FDA Website

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Iloperidone	Tablet	II (Paddle)	50	0.1 N Hydrochloric Acid	500	5, 10, 15, 30, 45, & 60 minutes	08/5/2010

Specification (firm's proposed): NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes

Specification (from RLD): NLT $\frac{(b)}{(4)}\%$ (Q) in 30 minutes¹

Reviewer's Note: the reviewer checked the NDA Annual report for the above mentioned specification for the RLD²

II.3 USP Method (if any): None

¹ DARRTS: NDA-022192: REV-CLINPHARM-01(General Review): 07/10/2008: JACKSON, ANDRE J

² DARRTS: NDA-022192: New/Annual Report with PMR/PMC Status: Annual Report-3: 06/29/2012

II.4 Summary of In vitro Dissolution data

Dissolution Conditions		Apparatus:	USP Type II (Paddle)									
		Speed of Rotation:	50 rpm									
		Medium:	0.1 N Hydrochloric Acid (b) (4)									
		Volume:	500 mL									
		Temperature:	37 °C ± 0.5°C									
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes										
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location
						5	10	15	30	45	60	
STP-1226-01	February 15, 2013	Iloperidone Tablets, 1 mg [Batch No.: G390057*] [Lupin Limited] Manufacturing Date: January 2013	1 mg, Tablets	12	Mean	81	90	93	96	96	96	m5.3.1.3
					Range	(b) (4)						
					%CV	7.89	4.52	4.29	2.83	2.28	2.51	
STP-1226-01	February 14, 2013	FANAPT® (iloperidone) Tablets, 1 mg (b) (4) Expiry Date: April 2015	1 mg, Tablets	12	Mean	94	96	96	97	97	97	
					Range	(b) (4)						
					%CV	3.10	3.53	4.44	3.66	3.01	3.29	

* Batch number G390074 is for 60's HDPE Bottle pack used in the bioequivalence (BE) studies and accordingly reflected in all BE study and related documents. It may be noted that the parent batch is G390057.

Note: The individual dissolution data on 12 units of test product and reference product is provided under [Section 5.3.1.3, Subpart 2.0](#).

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1227-01	February 16, 2013	Iloperidone Tablets, 2 mg [Batch No.: G390058] [Lupin Limited] Manufacturing Date: January 2013	2 mg, Tablets	12	Mean	79	88	92	94	98	97	m5.3.1.3	
					Range	(b) (4)							
					%CV	6.27	5.35	5.21	5.16	4.65	4.67		
STP-1227-01	March 21, 2013	FANAPT® (iloperidone) Tablets, 2 mg (b) (4)	2 mg, Tablets	12	Mean	81	90	93	96	96	97		
					Range	(b) (4)							
					%CV	6.60	4.80	3.17	2.36	1.44	2.03		

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1228-01	February 22, 2013	Iloperidone Tablets, 4 mg [Batch No.: G390061] [Lupin Limited] Manufacturing Date: January 2013	4 mg, Tablets	12	Mean	74	85	89	92	93	92	(b) (4)	
					Range								
					%CV	7.44	5.51	4.69	3.64	3.62	3.23		
STP-1228-01	March 23, 2012	FANAPT® (iloperidone) Tablets, 4 mg [Batch No.: HKTB] (b) (4) Expiry Date: May 2015	4 mg, Tablets	12	Mean	86	92	95	96	97	97	(b) (4)	
					Range								
					%CV	7.73	3.51	3.77	2.15	1.67	1.61		

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1229-01	February 18, 2013	Iloperidone Tablets, 6 mg [Batch No.: G390062] [Lupin Limited] Manufacturing Date: January 2013	6 mg, Tablets	12	Mean	77	89	95	99	101	102	(b) (4)	
					Range								
					%CV	7.37	4.89	2.94	3.01	2.65	3.63		
STP-1229-01	March 26, 2013	FANAPT® (iloperidone) Tablets, 6 mg [Batch No.: GVSK] (b) (4)	6 mg, Tablets	12	Mean	80	94	96	97	97	97	(b) (4)	
					Range								
					%CV	12.87	3.90	2.75	1.23	1.06	1.15		

[m5.3.1.3](#)

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1230-01	February 19, 2013	Iloperidone Tablets, 8 mg [Batch No.: G390063] [Lupin Limited] Manufacturing Date: January 2013	8 mg, Tablets	12	Mean	71	85	90	93	94	94	m5.3.1.3	
					Range	(b) (4)							
					%CV	7.54	4.29	2.66	1.68	1.56	1.54		
STP-1230-01	April 1, 2013	FANAPT® (iloperidone) Tablets, 8 mg [Batch No.: HPFG] (b) (4) Expiry Date: April 2015	8 mg, Tablets	12	Mean	83	89	88	96	99	100		
					Range	(b) (4)							
					%CV	7.68	6.58	7.02	3.42	3.12	3.26		

Dissolution Conditions		Apparatus:	USP Type II (Paddle)										
		Speed of Rotation:	50 rpm										
		Medium:	0.1 N Hydrochloric Acid (b) (4)										
		Volume:	500 mL										
		Temperature:	37 °C ± 0.5°C										
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes											
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location	
						5	10	15	30	45	60		
STP-1231-01	February 20, 2013	Iloperidone Tablets, 10 mg [Batch No.: G390064] [Lupin Limited] Manufacturing Date: January 2013	10 mg, Tablets	12	Mean	69	82	87	91	91	91	m5.3.1.3	
					Range	(b) (4)							
					%CV	7.27	5.25	3.92	3.82	3.14	2.75		
STP-1231-01	March 25, 2013	FANAPT® (iloperidone) Tablets, 10 mg [Batch No.: HBXW] (b) (4) Expiry Date: April 2014	10 mg, Tablets	12	Mean	70	80	87	92	95	96		
					Range	(b) (4)							
					%CV	15.06	10.03	7.14	4.35	2.63	1.98		

Dissolution Conditions		Apparatus:		USP Type II (Paddle)								
		Speed of Rotation:		50 rpm								
		Medium:		0.1 N Hydrochloric Acid (b) (4)								
		Volume:		500 mL								
		Temperature:		37 °C ± 0.5°C								
Firm's Proposed Specifications		Not Less Than (b) (4) % (Q) of the labeled amount of iloperidone dissolved in (b) (4) minutes										
Dissolution Testing Site (Name, Address)		Lupin Limited, Plot No.15-B, Phase 1-A, Verna Industrial Estate, Verna, Salcette, Goa –403 722 INDIA.										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)						Study Report Location
						5	10	15	30	45	60	
STP-1232-01	February 21, 2013	Iloperidone Tablets, 12 mg [Batch No.: G390065] [Lupin Limited] Manufacturing Date: January 2013	12 mg, Tablets	12	Mean	71	85	91	94	94	95	m5.3.1.3
					Range	(b) (4)						
					%CV	3.60	2.89	3.71	2.10	2.37	2.40	
STP-1232-01	March 7, 2013	FANAPT® (iloperidone) Tablets, 12 mg [Batch No. : HBHD] (b) (4) Expiry Date: April 2014	12 mg, Tablets	12	Mean	63	73	79	90	94	97	
					Range	(b) (4)						
					%CV	19.98	16.41	12.96	6.32	3.71	1.99	

Dissolution Method SOP effective at the time of testing (Yes/No)	yes
Were the drug product units pooled during the dissolution testing (Yes/No)?	no
Was the dissolution testing conducted on the bio-batch?	yes
Age of the test product at the time of dissolution testing.	about one month
Was the reference product expired at the time of dissolution testing (Yes/No)	no
Comments on the variability of the dissolution data	moderate to low variability
For two-stage dissolution testing, comment on the method of medium change from acid stage to buffer stage.	N/A

III. Reviewer's Comments for Dissolution Testing:

- There is no USP method for this product but there is an FDA-recommended method (in 500 mL of 0.1N HCl using apparatus II at 50 rpm). The firm, Lupin Limited, submitted comparative dissolution testing on its Iloperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths comparing it to (b) (4) Fanapt[®], 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths, using the FDA-recommended method. The firm's dissolution testing data with the FDA-recommended are acceptable.
- The firm proposed a specification of NLT (b) (4)% (Q) in (b) (4) minutes while the specification for the reference product is NLT (b) (4)% (Q) in 30 minutes. The dissolution of the test product is similar to the dissolution of the reference product across the strengths. The dissolution data of the bio-batch meet the specification for the reference product [NLT (b) (4)% (Q) in 30 minutes]. The dissolution data of 6 mg, 8 mg and 12 mg also meet the specification for the reference.
- The dissolution data of 4 mg strength meet the specification for the reference product, though on borderline [NLT (b) (4)% (Q) in 30 minutes, at S1³ level NLT (b) (4)%]. This is because of the dissolution data of the three units [#3 (b) (4)%, #7 (b) (4)% and #11 (b) (4)%] which reach it maximum dissolution at 30 minutes. The dissolution data of 2 mg strength, does not meet the specification for the reference product [NLT (b) (4)% (Q) in 30 minutes] at S1 level because of the dissolution data of one unit [#10 dissolves (b) (4)% at 30 minutes and (b) (4)% at 60 minutes]. Similarly, the dissolution data of 10 mg strength, does not meet the specification for the reference product [NLT (b) (4)% (Q) in 30 minutes] at S1 level because of the dissolution data of one unit [#11 dissolves (b) (4)% at 30 minutes and (b) (4)% at 60 minutes].
- It seems that the dissolution of some units of 2 mg, 4 mg and 10 mg strengths is incomplete and this is the possible reason for the dissolution data of these strengths not meeting the specification of the reference product [NLT (b) (4)% (Q) in 30 minutes] at S1 level. At the time of the review of the data the test product is more than twenty four (24) month old; therefore, repetition of the dissolution testing of these strengths using these old batches may not provide meaningful information. In addition the dissolution data of the bio-strength (1 mg) and the highest strength (12 mg), meet the specification of NLT (b) (4)% (Q) in 30 minutes. Therefore, at this stage a specification of NLT (b) (4)% (Q) in 30 minutes (same as the RLD specification) should be recommended for the test product. If the firm does not accept and acknowledge this specification then it should explain the reason for incomplete dissolution of some of the strengths and provide dissolution data of fresh batches to determine if reevaluation of the specification is warranted or not.

³ Though 12 unit data is considered.

- The Division of Bioequivalence (DB) recommends a more stringent specification: NLT (b)(4)% (Q) in 30 minutes. The firm provided data of the test product meet the DB recommended specification.

IV. Deficiency Comment for Dissolution Testing:

The firm's dissolution testing data with the FDA-recommended are acceptable. The firm's proposed specification, NLT (b)(4)% (Q) in (b)(4) minutes, is not acceptable. Based on the submitted data, the firm should acknowledge the FDA-recommended method and specification as follows:

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm
Temperature:	37°C ± 0.5°C
Media:	0.1 N Hydrochloric Acid
Volume:	500 mL
Specification:	NLT (b)(4)% (Q) dissolved in 30 minutes

V. Dissolution Recommendations:

The *in vitro* dissolution testing conducted by Lupin Limited, Iloperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg strengths comparing it to the RLD product, (b)(4) Fanapt[®], 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg strengths is **inadequate** due to the deficiency stated above.

VI. Individual Unit Data:

2.0 COMPARATIVE DISSOLUTION PROFILE (CONTINUED)

Table 2: Comparative Dissolution Profile in 0.1 N Hydrochloric Acid

FANAPT® (iloperidone) Tablets, 1 mg

Vs

Iloperidone Tablets, 1 mg [Lupin Limited]

Unit. No.	% Iloperidone Released											
	REFERENCE PRODUCT FANAPT® (iloperidone) Tablets, 1 mg [Batch No.: FFZN]						TEST PRODUCT Iloperidone Tablets, 1 mg [Batch No.: G390057] [Lupin Limited]					
	(b) (4)											
	Time (in Min)						Time (in Min)					
	5	10	15	30	45	60	5	10	15	30	45	60
1.	(b) (4)											
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												
Mean	94	96	96	97	97	97	81	90	93	96	96	96
Min.	(b) (4)											
Max.												
% RSD	3.10	3.53	4.44	3.66	3.01	3.29	7.89	4.52	4.29	2.83	2.28	2.51
Date of Analysis	February 14, 2013						February 15, 2013					
F2 Value	73.6											

min. – minutes; Max. – Maximum; Min. – Minimum, RSD – Relative Standard Deviation

2.0 COMPARATIVE DISSOLUTION PROFILE (CONTINUED)

Table 3: Comparative Dissolution Profile in 0.1 N Hydrochloric Acid (b) (4)

FANAPT® (loperidone) Tablets, 2 mg (b) (4)

Vs

loperidone Tablets, 2 mg [Lupin Limited]

Unit. No.	% Iloperidone Released											
	REFERENCE PRODUCT FANAPT® (iloperidone) Tablets, 2 mg [Batch No.: HKSY] (b) (4)						TEST PRODUCT Iloperidone Tablets, 2 mg [Batch No.: G390058] [Lupin Limited]					
	Time (in Min)						Time (in Min)					
	5	10	15	30	45	60	5	10	15	30	45	60
1.	(b) (4)											
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												
Mean	81	90	93	96	96	97	79	88	92	94	98	97
Min.	(b) (4)											
Max.												
% RSD	6.60	4.80	3.17	2.36	1.44	2.03	6.27	5.35	5.21	5.16	4.65	4.67
Date of Analysis	March 21, 2013						February 16, 2013					
F2 Value	85.4											

min. – minutes; Max. – Maximum; Min. – Minimum, RSD - Relative Standard Deviation

2.0 COMPARATIVE DISSOLUTION PROFILE (CONTINUED)

Table 4: Comparative Dissolution Profile in 0.1 N Hydrochloric Acid (Deaerated)

FANAPT® (loperidone) Tablets, 4 mg (b) (4)

Vs

loperidone Tablets, 4 mg [Lupin Limited]

Unit. No.	% Iloperidone Released											
	REFERENCE PRODUCT FANAPT® (iloperidone) Tablets, 4 mg [Batch No.: HKTBI] (b) (4)						TEST PRODUCT Iloperidone Tablets, 4 mg [Batch No.: G390061] [Lupin Limited]					
	Time (in Min)						Time (in Min)					
	5	10	15	30	45	60	5	10	15	30	45	60
1.	(b) (4)											
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												
Mean	86	92	95	96	97	97	74	85	89	92	93	92
Min.	(b) (4)											
Max.												
% RSD	7.73	3.51	3.77	2.15	1.67	1.61	7.44	5.51	4.69	3.64	3.62	3.23
Date of Analysis	March 23, 2012						February 22, 2013					
F2 Value	57.8											

min. – minutes; Max. – Maximum; Min. – Minimum, RSD - Relative Standard Deviation

2.0 COMPARATIVE DISSOLUTION PROFILE (CONTINUED)

Table 5: Comparative Dissolution Profile in 0.1 N Hydrochloric Acid (b) (4)
FANAPT® (iloperidone) Tablets, 6 mg (b) (4)

Vs
Iloperidone Tablets, 6 mg [Lupin Limited]

Unit. No.	% Iloperidone Released											
	REFERENCE PRODUCT FANAPT® (iloperidone) Tablets, 6 mg [Batch No.: GVSK] (b) (4)						TEST PRODUCT Iloperidone Tablets, 6 mg [Batch No.: G390062] [Lupin Limited]					
	Time (in Min)						Time (in Min)					
	5	10	15	30	45	60	5	10	15	30	45	60
1.	(b) (4)											
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												
Mean	80	94	96	97	97	97	77	89	95	99	101	102
Min.	(b) (4)											
Max.												
% RSD	12.87	3.90	2.75	1.23	1.06	1.15	7.37	4.89	2.94	3.01	2.65	3.63
Date of Analysis	March 26, 2013						February 18, 2013					
F2 Value	71.1											

min. – minutes; Max. – Maximum; Min. – Minimum, RSD – Relative Standard Deviation

2.0 COMPARATIVE DISSOLUTION PROFILE (CONTINUED)

Table 6: Comparative Dissolution Profile in 0.1 N Hydrochloric Acid

FANAPT® (iloperidone) Tablets, 8 mg

Vs

Iloperidone Tablets, 8 mg [Lupin Limited]

Unit. No.	% Iloperidone Released											
	REFERENCE PRODUCT FANAPT® (iloperidone) Tablets, 8 mg [Batch No.: HPEG] (b) (4)						TEST PRODUCT Iloperidone Tablets, 8 mg [Batch No.: G390063] [Lupin Limited]					
	Time (in Min)						Time (in Min)					
	5	10	15	30	45	60	5	10	15	30	45	60 (b) (4)
1.												
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												
Mean	83	89	88	96	99	100	71	85	90	93	94	94 (b) (4)
Min.												
Max.												
% RSD	7.68	6.58	7.02	3.42	3.12	3.26	7.54	4.29	2.66	1.68	1.56	1.54
Date of Analysis	April 1, 2013						February 19, 2013					
F2 Value	60.0											

min. – minutes;

Max. – Maximum; Min. – Minimum,

RSD - Relative Standard Deviation

2.0 COMPARATIVE DISSOLUTION PROFILE (CONTINUED)

Table 7: Comparative Dissolution Profile in 0.1 N Hydrochloric Acid

FANAPT® (iloperidone) Tablets, 10 mg

Vs

Iloperidone Tablets, 10 mg [Lupin Limited]

Unit. No.	% Iloperidone Released											
	REFERENCE PRODUCT FANAPT® (iloperidone) Tablets, 10 mg [Batch No.: HBXW]						TEST PRODUCT Iloperidone Tablets, 10 mg [Batch No.: G390064] [Lupin Limited]					
	(b) (4)											
	Time (in Min)						Time (in Min)					
	5	10	15	30	45	60	5	10	15	30	45	60
1.	(b) (4)											
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												
Mean	70	80	87	92	95	96	69	82	87	91	91	91
Min.	(b) (4)											
Max.												
% RSD	15.06	10.03	7.14	4.35	2.63	1.98	7.27	5.25	3.92	3.82	3.14	2.75
Date of Analysis	March 25, 2013						February 20, 2013					
F2 Value	76.4											

min. – minutes; Max. – Maximum; Min. – Minimum, RSD - Relative Standard Deviation

2.0 COMPARATIVE DISSOLUTION PROFILE (CONTINUED)

Table 8: Comparative Dissolution Profile in 0.1 N Hydrochloric Acid (b) (4)

FANAPT® (iloperidone) Tablets, 12 mg [Novartis Pharmaceutical Corporation]

Vs

Iloperidone Tablets, 12 mg [Lupin Limited]

Unit. No.	% Iloperidone Released											
	REFERENCE PRODUCT FANAPT® (iloperidone) Tablets, 12 mg [Batch No.: HBHD] (b) (4)						TEST PRODUCT Iloperidone Tablets, 12 mg [Batch No.: G390065] [Lupin Limited]					
	Time (in Min)						Time (in Min)					
	5	10	15	30	45	60	5	10	15	30	45	60 (b) (4)
1.												
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												
Mean	63	73	79	90	94	97	71	85	91	94	94	95 (b) (4)
Min.												
Max.												
% RSD	19.98	16.41	12.96	6.32	3.71	1.99	3.60	2.89	3.71	2.10	2.37	2.40
Date of Analysis	March 7, 2013						February 21, 2013					
F2 Value	55.0											

min. – minutes; Max. – Maximum; Min. – Minimum, RSD - Relative Standard Deviation

BIOEQUIVALENCE DEFECIENCY TO BE PROVIDED TO THE APPLICANT
(PROCESSED BY BIO-PM)
EASILY CORRECTABLE DEFICIENCY-10 (ECD-10).

ANDA: 206890

APPLICANT: Lupin Limited

DRUG PRODUCT: Iloperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg,
10 mg, and 12 mg

The Division of Bioequivalence (DB) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) studies and the waiver requests will be conducted later.

Your dissolution testing using the FDA-recommended method is acceptable. However, your proposed specification, NLT (b)(4) % (Q) in (b)(4) minutes, is not acceptable. Please acknowledge the following FDA-recommended dissolution method and specification:

USP Apparatus:	II (paddle)
Rotational Speed:	50 rpm
Temperature:	37°C ± 0.5°C
Media:	0.1 N Hydrochloric Acid
Volume:	500 mL
Specification:	NLT (b)(4) % (Q) dissolved in 30 minutes

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D. R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

VII. OUTCOME

ANDA:

Enter Review Productivity and Generate Report

<http://cdsogd1/bioprod>

APPEARS THIS WAY ON
ORIGINAL