CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 207231

Name: Iloperidone (Tablet), 1MG, 2MG, 4MG, 6MG, 8MG 10MG, 12MG

Sponsor: Iventia

Approval Date: November 28, 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207231

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 207231

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207231

ANDA APPROVAL

SciRegs International, Inc.
U.S. Agent for Inventia Healthcare Private Limited
6333 Summercrest Drive
Columbia, MD 21045
Attention: C. Jeanne Taborsky
Regulatory Affairs Agent

Dear Madam:

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

Reference is also made to the tentative approval letter issued by the Agency on June 27, 2016, and to your amendments dated August 16 and November 8, 2016.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. **Accordingly the ANDA is approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Iloperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg, to be bioequivalent and, therefore, 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). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The reference listed drug (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.S. Patent Number	Expiration Date
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 under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents[1] are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Iloperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. You have notified the agency that Inventia Healthcare Private Limited (Inventia) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that litigation for infringement of the '610 patent was brought against Inventia in the United States District Court for the District of Delaware [Vanda Pharmaceuticals Inc. v. Inventia Healthcare PVT Ltd., Civil Action No. 1:15-cv-00362] and in the Unites States District Court for Northern District of West Virginia [Vanda Pharmaceuticals Inc. v. Inventia Healthcare PVT Ltd., Civil Action No: 3:15-cv-00059], and for infringement of the '432 patent in the United States District Court for the District of Delaware [Vanda Pharmaceuticals Inc. v. Inventia Healthcare PVT Ltd., Civil Action no.1:15-cv-00921].

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 & 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.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions 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 1 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

[1] The agency notes that the '610, '432, '776, '638, '742, '254, '255, '256, 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.

forms (FDFs) or active pharmaceutical ingredients (APIs) 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.

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 http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

Carol A. Holquist, RPh
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Carol Holquist

Digitally signed by Carol Holquist
Date: 11/28/2016 10:38:20AM
GUID: 508da712000293e0f6d8acfd3c5e67fe

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207231

LABELING

33 mm

ILOPERIDONE tablets, for oral use

Space for Pharma code

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, for oral use

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

Contraindications (4) 1/2016

INDICATIONS AND USAGE

Iloperidone tablets are an atypical antipsychotic agent indicated for the treatment of schizophrenia in adults. (1, 14) In choosing among treatments, prescribers should consider the ability of iloperidone tablets to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate iloperidone tablets slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration. (2, 5, 14)

DOSAGE AND ADMINISTRATION

The recommended target dosage of iloperidone 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. 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, 6.2)

WARNINGS AND PRECAUTIONS

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack). (5.2)
- 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, 5.3, 7.1, 7.3, 12.3)
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation of drug and close monitoring. (5.4)
- Tardive dyskinesia: Discontinue if clinically appropriate. (5.5)
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain. (5.6)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold. (5.7)
- Orthostatic hypotension: Dizziness, tachycardia, and syncope can occur with standing. (5.8)
- 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. (5.9)
- Suicide: Close supervision of high risk patients. (5.13)
- Priapism: Cases have been reported in association with iloperidone treatment. (5.14)
- Potential for cognitive and motor impairment: Use caution when operating machinery. (5.15)

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence ≥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 Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX). or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- Lactation: Advise not to breast feed. (8.2)
- Pediatric Use: Safety and effectiveness not established in children and adolescents. (8.4)
- Hepatic Impairment: Iloperidone is not recommended for severe patients with 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: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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. 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 schizophrenia in adults.

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 (5.3)]*. 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 tablets 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 tablets. 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)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dose

Iloperidone 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 orally twice daily. Dose increases to reach the target range of 6 to 12 mg twice daily (12 to 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 tablets doses above 24 mg/day have not been systematically evaluated in the clinical trials. Efficacy was demonstrated with iloperidone tablets 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 *[see Adverse Reactions (6.1)]*.

Iloperidone tablets can be administered without regard to meals.

2.2 Dosage in Special Populations

Dosage adjustment for patients taking iloperidone 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)]*.

Dosage adjustment for patients taking iloperidone 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)]*.

Dosage adjustment for patients taking iloperidone 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. Patients with moderate hepatic impairment may require dose reduction, if clinically indicated. Iloperidone is not recommended for patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

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.

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. The tablets are white to off white, round, flat with beveled edges uncoated tablet, debossed with **"050", "051", "052", "053", "054", "055", or "056"** on one side and plain on other side.

4 CONTRAINDICATIONS

Iloperidone is contraindicated in individuals with a known hypersensitivity reaction to the product. Anaphylaxis, angioedema, and other hypersensitivity reactions have been reported *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all cause risk of death in elderly patients with dementia related psychosis. Analyses of 17 dementia related psychosis placebo controlled trials (modal duration of 10 weeks and 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 that 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 placebo treated patients.

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. Iloperidone is not approved for the treatment of patients with dementia related psychosis *[see Boxed Warning, Warnings and Precautions (5.2)]*.

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. Iloperidone tablets are not approved for the treatment of patients with dementia related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.

5.3 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 tablets 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.

5.4 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.

5.5 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.

5.6 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. 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 hyperglycemia related adverse events in patients treated with the atypical antipsychotics included in these studies.

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 Tablets 24 mg/day
	Mean Change from Baseline(mg/dL)	
Serum Glucose Change from Baseline	n=114	n=228
	-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 to 6 months	6 to 12 months	>12 months
Iloperidone Tablets 10 to 16 mg/day	1.8 (N 773)	5.4 (N 723)	5.4 (N 425)
Iloperidone Tablets 20 to 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 Tablets 24 mg/day
	Mean Change from Baseline (mg/dL)	
Cholesterol	n= 114	n=228
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 (<200 mg/dL to ≥240 mg/dL)	1.4 % (1/72)	3.6 % (5/141)
LDL Normal to High (<100 mg/dL to ≥160 mg/dL)	2.4% (1/42)	1.1% (1/90)
HDL Normal to Low (≥40 mg/dL to <40 mg/dL)	23.8% (19/80)	12.1% (20/166)
Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	8.3% (6/72)	10.1% (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 to 6 months	6 to 12 months	>12 months
Iloperidone Tablets 10 to 16 mg/day	-3.9 (N 783)	-3.9 (N 726)	-7.7 (N 428)
Iloperidone Tablets 20 to 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 to 6 months	6 to 12 months	>12 months
Iloperidone Tablets 10 to 16 mg/day	-8.9 (N 783)	-8.9 (N 726)	-17.7 (N 428)
Iloperidone Tablets 20 to 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 ≥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

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

5.7 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. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.8 Orthostatic Hypotension and Syncope

Iloperidone can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. This reflects its alpha1 adrenergic 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% (5/1,344) of patients treated with iloperidone, compared with 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 5% of patients given 20 to 24 mg/day, 3% of patients given 10 to 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.

5.9 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 <1,000/mm^3) should discontinue iloperidone and have their WBC followed until recovery.

5.10 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)]*. 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 tablets 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 3,210 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.

5.11 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.

5.12 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. Iloperidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Boxed Warning]*.

5.13 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.

5.14 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.

5.15 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 2,070 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.

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 mg 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 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 Adverse Reactions in Short-Term, Fixed- or Flexible-Dose, Placebo-Controlled Trials in Adult Patients*

Body System or Organ Class	Placebo	Iloperidone Tablets 10 to 16 mg/day	Iloperidone Tablets 20 to 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 tablets 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 to 24 mg/day were twice than the incidence in patients treated with iloperidone 10 to 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 ≥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 to 24 mg/day as on 10 to 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 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

Adverse Event Term	Placebo (%) (N=587)	Iloperidone Tablets 10 to 16 mg/day (%) (N=483)	Iloperidone Tablets 20 to 24 mg/day (%) (N=391)
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.

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% (13/1,342) 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 adverse reactions in patients treated with iloperidone at multiple doses ≥ 4 mg/day during any phase of a trial with the database of 3,210 iloperidone treated patients. All reported reactions are included except those already listed in Table 7, or other parts of the *Adverse Reactions (6)*, 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.

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 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 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 post approval use of iloperidone: retrograde ejaculation and hypersensitivity reactions (including anaphylaxis; angioedema; throat tightness; oropharyngeal swelling; swelling of the face, lips, mouth, and tongue; urticaria; rash; and pruritus). 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 alpha1 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 to 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: Co administration 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 to 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 to 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 to 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 (5.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to iloperidone during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1 866 961 2388 or visit http://womensmentalhealth.org/clinical and research programs/pregnancyregistry/.

Risk Summary
Neonates whose mothers are exposed to antipsychotic drugs, including iloperidone, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *[see Clinical Considerations]*. The limited available data with iloperidone in pregnant women are not sufficient to inform a drug associated risk for major birth defects and miscarriage. Iloperidone was not teratogenic when administered orally to pregnant rats during organogenesis at doses up to 26 times the maximum recommended human dose of 24 mg/day on mg/m^2 basis. However, it prolonged the duration of pregnancy and parturition, increased still births, early intrauterine deaths, increased incidence of developmental delays, and decreased post partum pup survival. Iloperidone was not teratogenic when administered orally to pregnant rabbits during organogenesis at doses up to 20 times the MRHD on mg/m^2 basis. However, it increased early intrauterine deaths and decreased fetal viability at term at the highest dose which was also a maternally toxic dose *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates whose mothers were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.
Data
Animal Data
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.

8.2 Lactation
Risk Summary
There is no information regarding the presence of iloperidone or its metabolites in human milk, the effects of iloperidone on a breastfed child, nor the effects of iloperidone on human milk production. Iloperidone is present in rat milk *[see Data]*. Because of the potential for serious adverse reactions in breastfed infants, advise a woman not to breastfeed during treatment with iloperidone.

Data
The transfer of radioactivity into the milk of lactating rats was investigated following a single dose of [14C] iloperidone at 5 mg/kg. The concentration of radioactivity in milk at 4 hours post dose was near 10 fold greater than that in plasma at the same time. However, by 24 hours after dosing, concentrations of radioactivity in milk had fallen to values slightly lower than plasma. The metabolic profile in milk was qualitatively similar to that in plasma.

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 3,210 patients treated with iloperidone in premarketing trials, 25 (0.5%) were ≥65 years old and there were no patients ≥75 years old.

Elderly patients with dementia related psychosis treated with iloperidone 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 and Warnings and Precautions (5.1, 5.2)]*.

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. $AUC_{0-\infty}$ 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 iloperidone is needed in patients with mild hepatic impairment. Patients with moderate hepatic impairment may require dose reduction. Iloperiodne is not recommended for patients with severe hepatic impairment *[see Dosage and Administration (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.

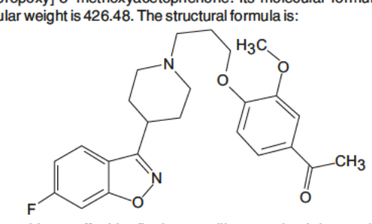
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Iloperidone is not a controlled substance.

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 3,210 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 an atypical antipsychotropic 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 finely crystalline 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, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium bicarbonate and purified water (removed during processing). The tablets are white to off white, round, flat with beveled edges uncoated tablet, debossed with **"050", "051", "052", "053", "054", "055", or "056"** on one side and plain on other side.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The mechanism of action of iloperidone in schizophrenia is unknown. However the efficacy of iloperidone could be mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 (5 HT_2) antagonism. Iloperidone forms an active metabolite, P88, that has an in vitro receptor binding profile similar to the parent drug.

12.2 Pharmacodynamics
Iloperidone acts as an antagonist with high (nM) affinity binding to serotonin 5 HT_{2A} dopamine D_2 and D_3 receptors, and norepinephrine $NE_{\alpha 1}$ receptors (K_i values of 5.6, 6.3, 7.1, and 0.36 nM, respectively). Iloperidone has moderate affinity for dopamine D_4, and serotonin 5 HT_6 and 5 HT_7 receptors (K_i values of 25, 43, and 22, nM respectively), and low affinity for the serotonin 5 HT_{1A}, dopamine D_1, and histamine H_1 receptors (K_i values of 168, 216 and 437 nM, respectively). Iloperidone has no appreciable affinity (K_i>1,000 nM) for cholinergic muscarinic receptors. The affinity of the iloperidone metabolite P88 is generally equal or less than that of the parent compound, while the metabolite P95 only shows affinity for 5 HT_{2A} (K_i value of 3.91) and the $NE\alpha_{1A}$, $NE\alpha_{1B}$, $NE\alpha_{1D}$, and $NE\alpha_{2C}$ 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 to 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 1,340 to 2,800 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.
Co administration 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/m^2 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.

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 MRHD of 24 mg/day on a mg/m^2 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 to 16 mg/day or 20 to 24 mg/day) compared to placebo and an active control (risperidone). For the 12 to 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 to 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 to 16 mg/day and the 20 to 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 tablets 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 white to off white, round, flat with beveled edges uncoated tablet, debossed with **"050", "051", "052", "053", "054", "055", or "056"** on one side and plain on other side. Tablets are supplied in the following strengths and package configurations:

Package Configuration	Tablet Strength (mg)	NDC Code
Bottles of 60	1 mg	0378-0630-91
Bottles of 100		0378-0630-01
Cartons of 100 (10x10's) Unit dose blister		0378-0630-88
Bottles of 60	2 mg	0378-0631-91
Bottles of 100		0378-0631-01
Cartons of 100 (10x10's) Unit dose blister		0378-0631-88
Bottles of 60	4 mg	0378-0632-91
Bottles of 100		0378-0632-01
Cartons of 100 (10x10's) Unit dose blister		0378-0632-88
Bottles of 60	6 mg	0378-0633-91
Bottles of 100		0378-0633-01
Cartons of 100 (10x10's) Unit dose blister		0378-0633-88
Bottles of 60	8 mg	0378-0634-91
Bottles of 100		0378-0634-01
Cartons of 100 (10x10's) Unit dose blister		0378-0634-88
Bottles of 60	10 mg	0378-0635-91
Bottles of 100		0378-0635-01
Cartons of 100 (10x10's) Unit dose blister		0378-0635-88
Bottles of 60	12 mg	0378-0636-91
Bottles of 100		0378-0636-01
Cartons of 100 (10x10's) Unit dose blister		0378-0636-88

Storage : Store iloperidone tablets at 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:

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 tablets with other drugs that cause QT interval prolongation *[see Warnings and Precautions (5.3)]*. Patients should be told to inform physicians that they are taking iloperidone tablets before any new drug is taken.

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 tablets. 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 (5.4)]*.

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 tablets. Clinical monitoring of weight is recommended. *[see Warnings and Precautions (5.6)]*.

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 (5.8)]*.

Interference with Cognitive and Motor Performance
Because iloperidone tablets 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 tablets therapy does not affect them adversely *[see Warnings and Precautions (5.15)]*.

Pregnancy
Advise patients that third trimester use of iloperidone may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients to notify their healthcare provider with known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Pregnancy Registry
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to iloperidone during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation
Advise women not to breastfeed during treatment with iloperidone *[see Use in Specific Populations (8.2)]*.

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)]*.

Alcohol
Patients should be advised to avoid alcohol while taking iloperidone tablets.

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

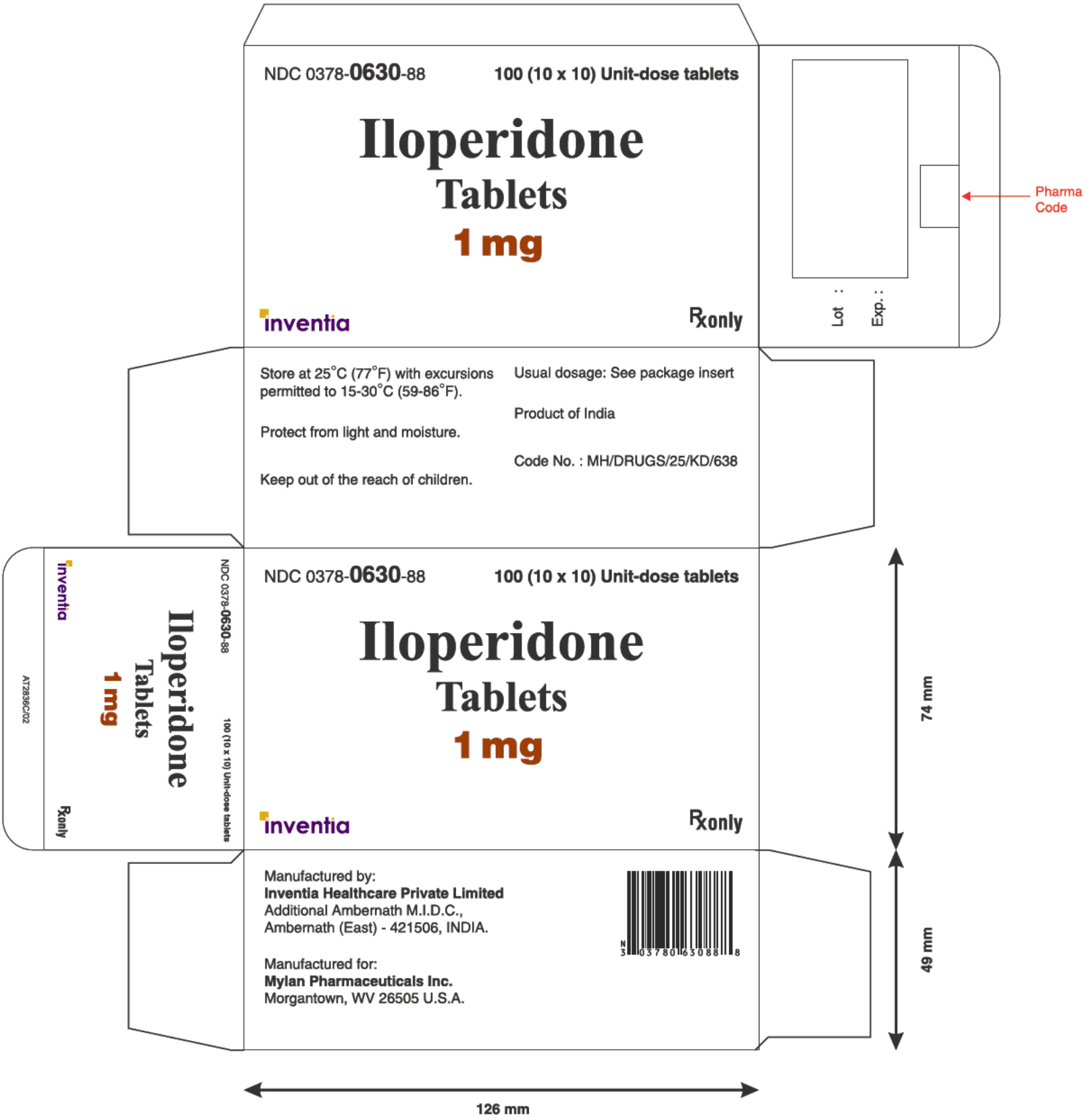
Manufactured By:
Inventia Healthcare Private Limited
Plot No.F1 & F 1/1, Additional Ambernath M.I.D.C.,
Ambernath (East) 421506,
Dist. Thane, Maharashtra, India

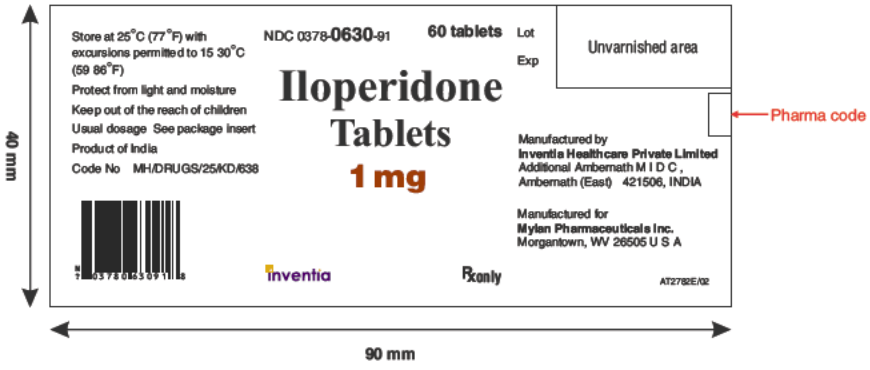
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

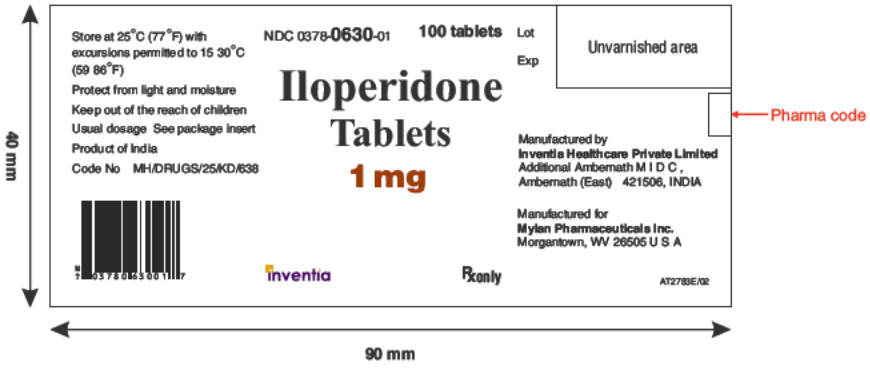
October 2016

AT2836L/04

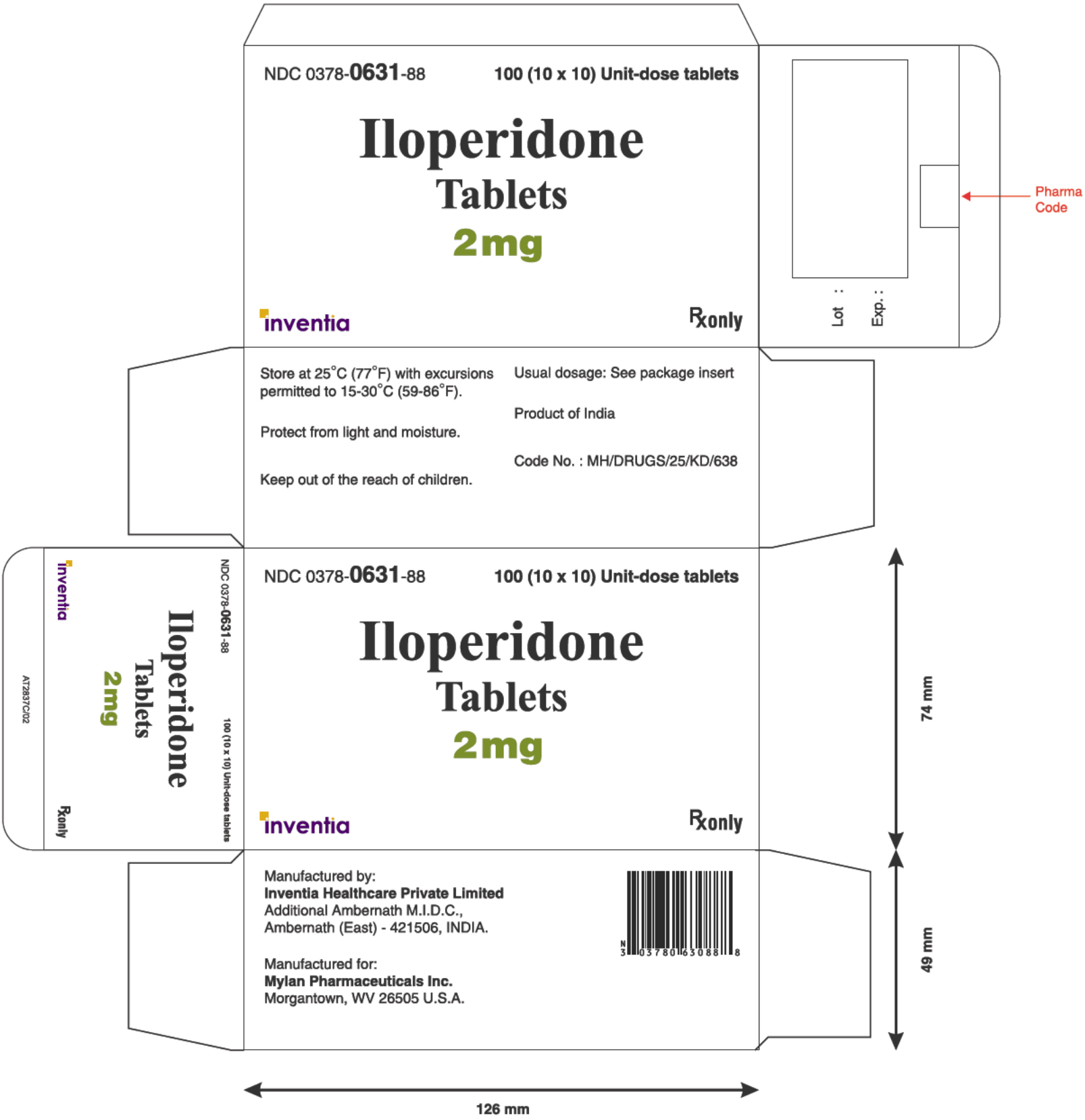

Code No MH/DRUGS/25/KD/638
AT2836T/02
Iloperidone
Tablet
1 mg
Lot
Exp
Product of India
inventia
120 mm
70 mm

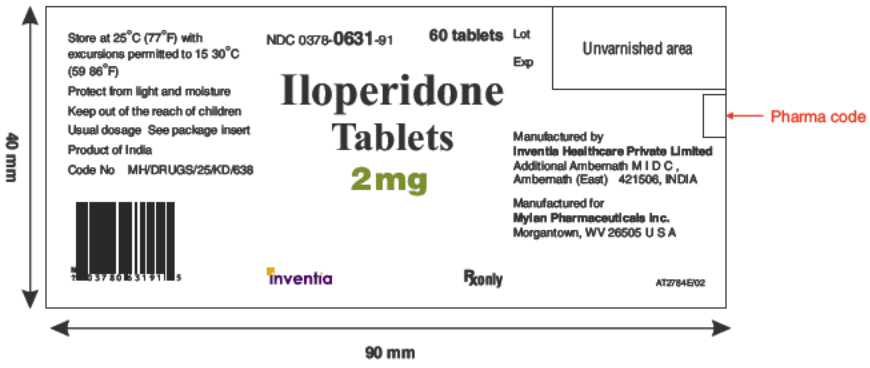

NDC 0378-0630-88
100 (10 x 10) Unit-dose tablets
Iloperidone
Tablets
1 mg
inventia
Rxonly
Lot :
Exp. :
Pharma Code
Store at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).
Protect from light and moisture.
Keep out of the reach of children.
Usual dosage: See package insert
Product of India
Code No. : MH/DRUGS/25/KD/638
AT2836C/02
74 mm
49 mm
Manufactured by:
Inventia Healthcare Private Limited
Additional Ambernath M.I.D.C.,
Ambernath (East) - 421506, INDIA.
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
126 mm

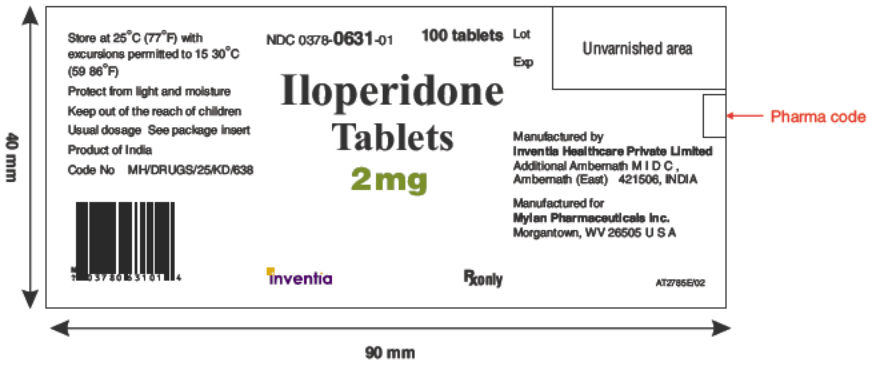

Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0630-91
60 tablets
Lot
Exp
Unvarnished area
Iloperidone
Tablets
1 mg
Pharma code
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2782E/02
40 mm
90 mm


Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0630-01
100 tablets
Lot
Exp
Unvarnished area
Iloperidone
Tablets
1 mg
Pharma code
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2783E/02
40 mm
90 mm

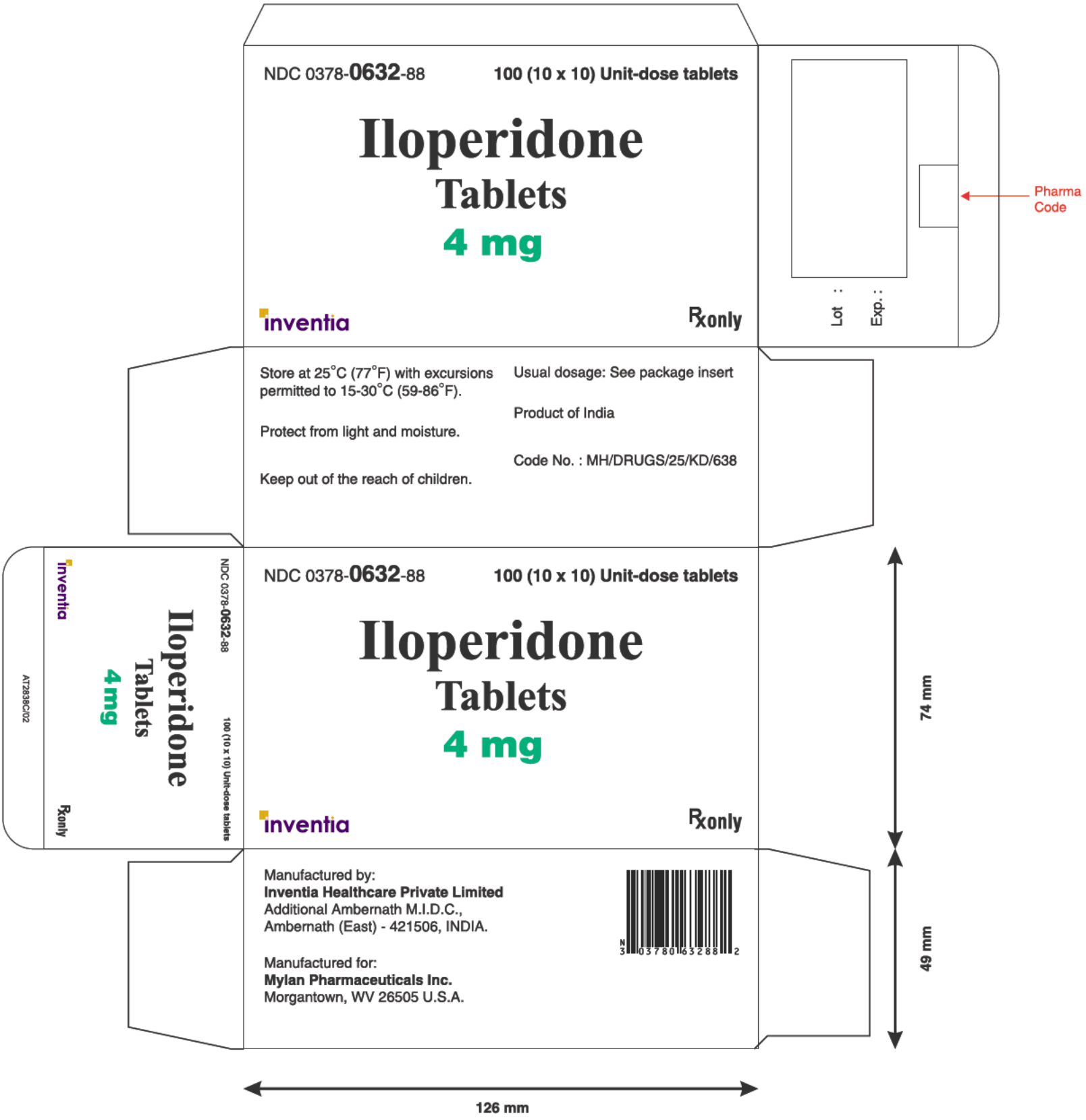

Code No MH/D RUSS/25/KD/938
AT 28.37 T/01
Iloperidone
Tablet
2 mg
Lot
Exp
inventia
Product of India
70 mm

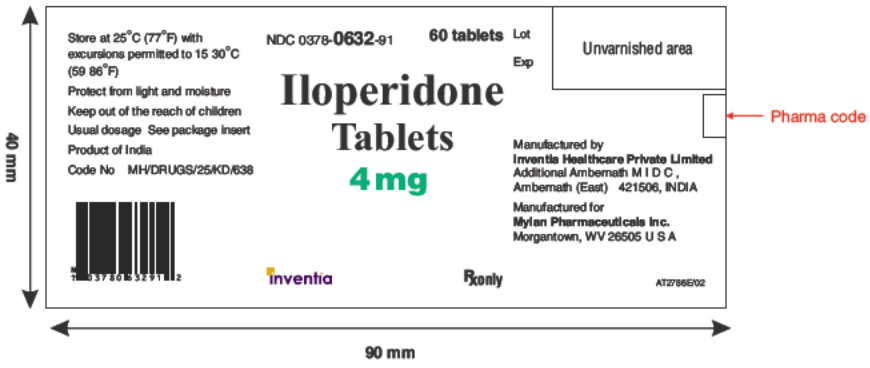

NDC 0378-0631-88
100 (10 x 10) Unit-dose tablets
Iloperidone
Tablets
2mg
inventia
Rxonly
Lot :
Exp. :
Pharma Code
Store at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).
Protect from light and moisture.
Keep out of the reach of children.
Usual dosage: See package insert
Product of India
Code No. : MH/DRUGS/25/KD/638
AT2837C/02
74 mm
49 mm
Manufactured by:
Inventia Healthcare Private Limited
Additional Ambernath M.I.D.C.,
Ambernath (East) - 421506, INDIA.
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
126 mm

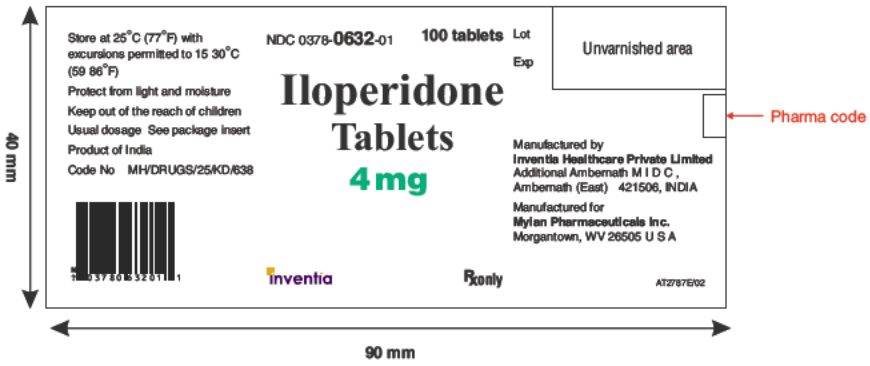

Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0631-91
60 tablets
Lot
Exp
Unvarnished area
Pharma code
Iloperidone
Tablets
2mg
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2784E/02
40 mm
90 mm

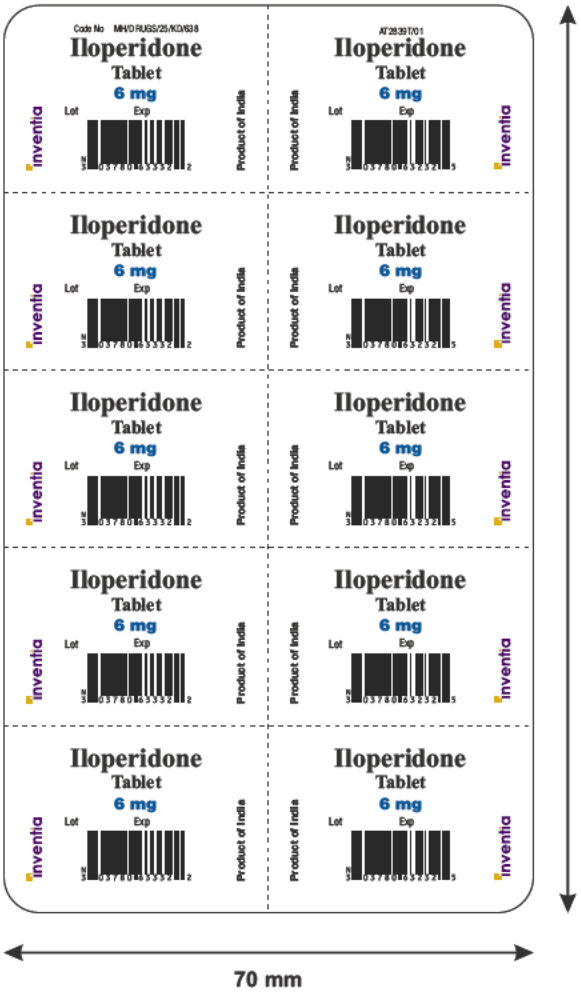

Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0631-01
100 tablets
Lot
Exp
Unvarnished area
Iloperidone Tablets
2mg
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
Pharma code
inventia
Rx only
AT2785E/02
40 mm
90 mm

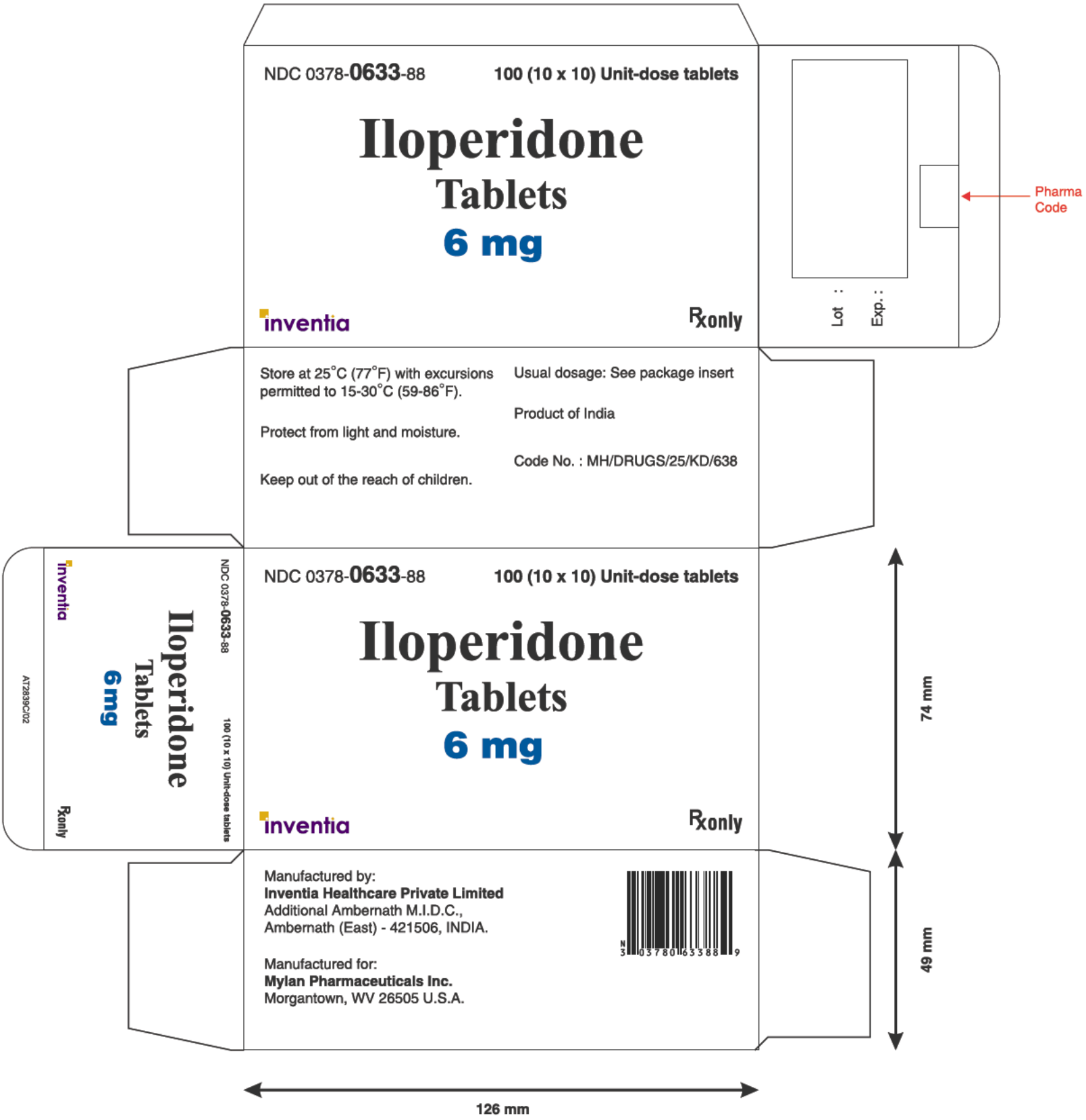

Code No MH/D RUSS/25/KD/938
AT 2838 T/01
Iloperidone
Tablet
4 mg
Lot
Exp
inventia
Product of India
70 mm

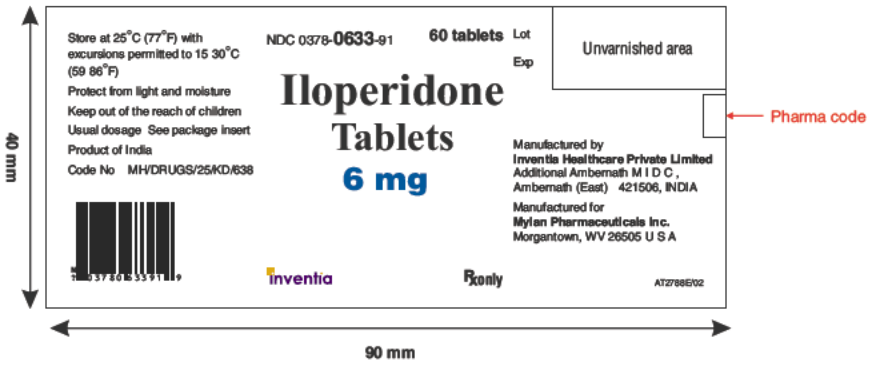

NDC 0378-0632-88
100 (10 x 10) Unit-dose tablets
Iloperidone
Tablets
4 mg
inventia
Rxonly
Lot :
Exp. :
Pharma Code
Store at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).
Protect from light and moisture.
Keep out of the reach of children.
Usual dosage: See package insert
Product of India
Code No. : MH/DRUGS/25/KD/638
AT2838C/02
74 mm
49 mm
Manufactured by:
Inventia Healthcare Private Limited
Additional Ambernath M.I.D.C.,
Ambernath (East) - 421506, INDIA.
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
126 mm

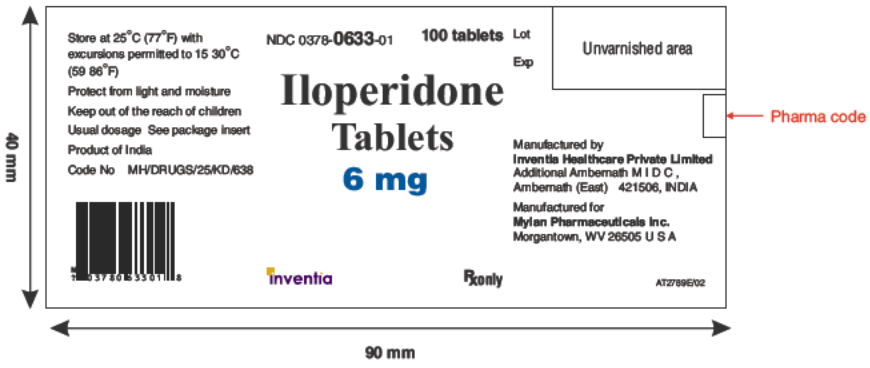

Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0632-91
60 tablets
Lot
Exp
Iloperidone Tablets
4 mg
Unvarnished area
Pharma code
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2786E/02
40 mm
90 mm

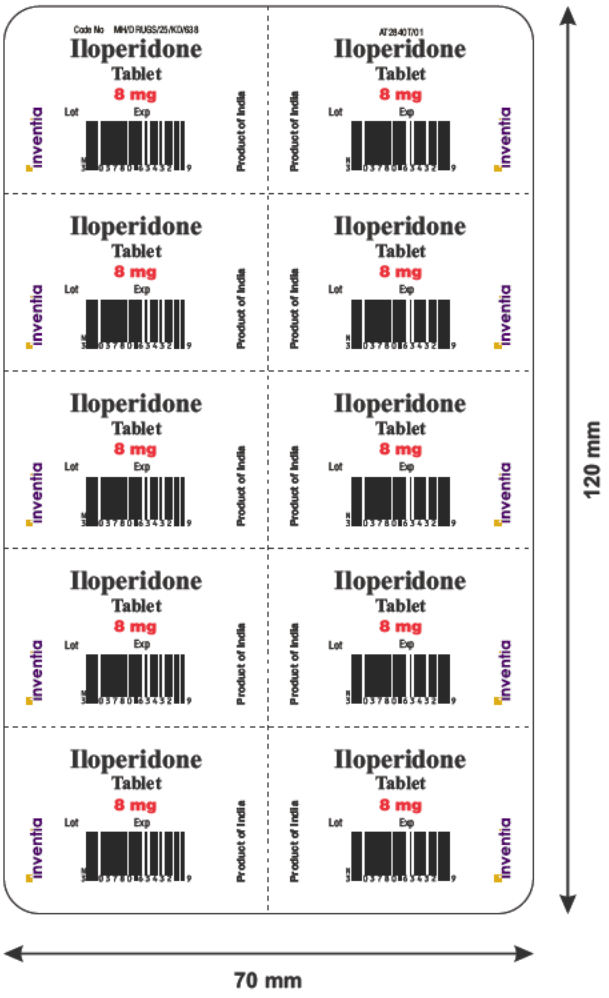

Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0632-01
100 tablets
Lot
Exp
Iloperidone Tablets
4 mg
Unvarnished area
Pharma code
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2787E/02
40 mm
90 mm

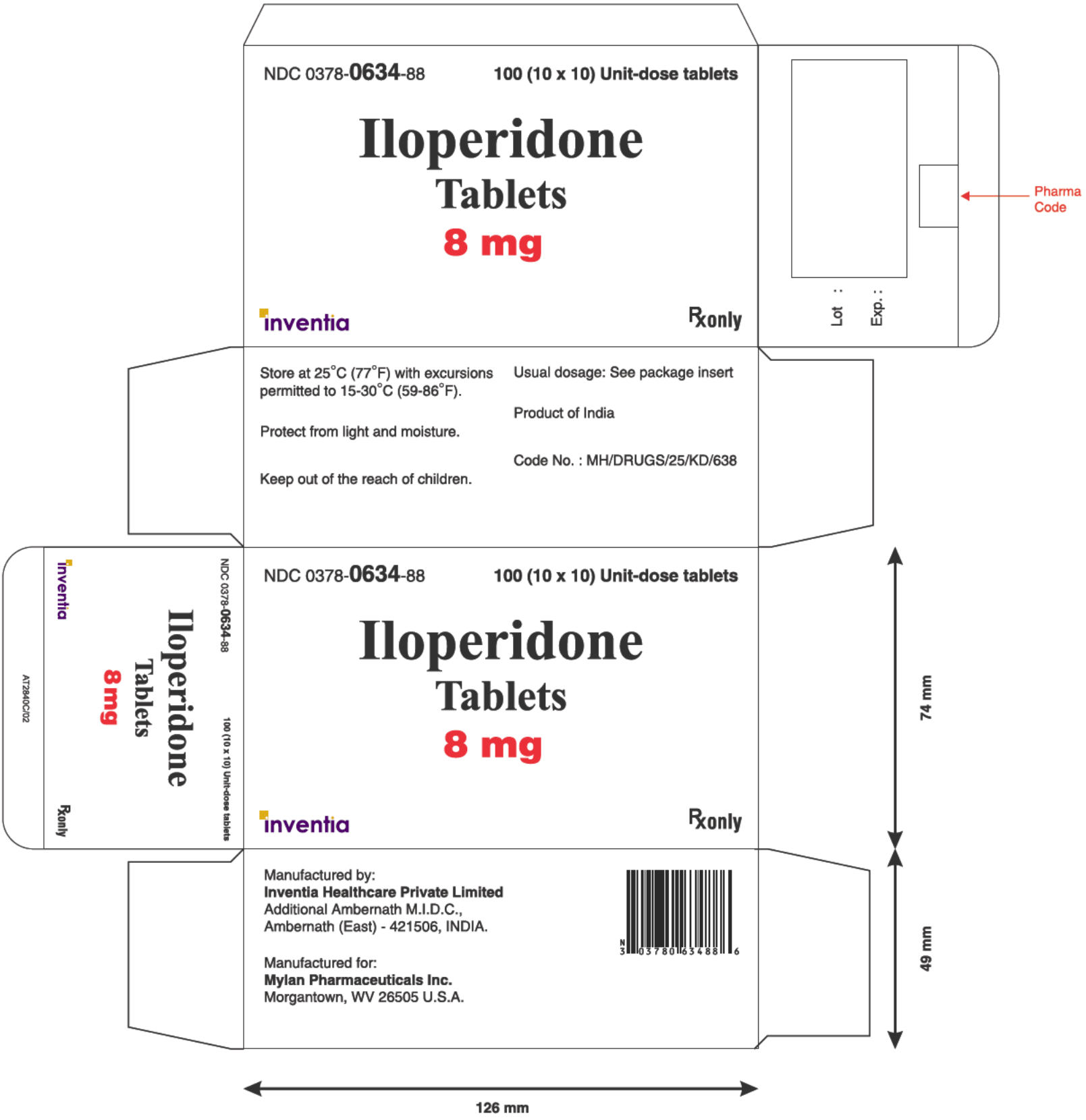

Code No MH/D RUSS/25/KD/938
AT 2839T/01
Iloperidone
Tablet
6 mg
Lot
Exp
inventia
Product of India
70 mm

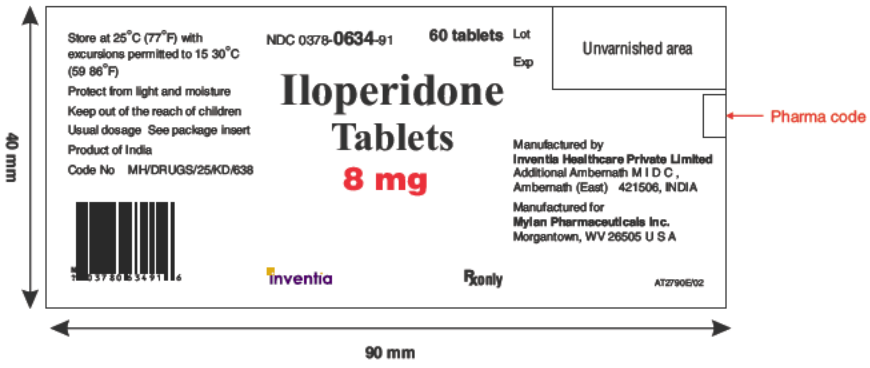

NDC 0378-0633-88
100 (10 x 10) Unit-dose tablets
Iloperidone
Tablets
6 mg
inventia
Rxonly
Lot :
Exp. :
Pharma Code
Store at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).
Protect from light and moisture.
Keep out of the reach of children.
Usual dosage: See package insert
Product of India
Code No. : MH/DRUGS/25/KD/638
Manufactured by:
Inventia Healthcare Private Limited
Additional Ambernath M.I.D.C.,
Ambernath (East) - 421506, INDIA.
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
AT2839C/02
74 mm
49 mm
126 mm

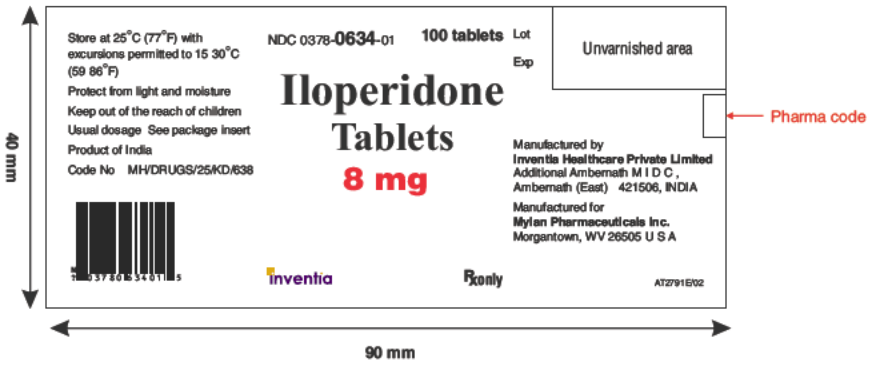

Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0633-91
60 tablets
Lot
Exp
Iloperidone Tablets
6 mg
Unvarnished area
Pharma code
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2786E/02
40 mm
90 mm


Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0633-01
100 tablets
Lot
Exp
Iloperidone Tablets
6 mg
Unvarnished area
Pharma code
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2789E/02
40 mm
90 mm

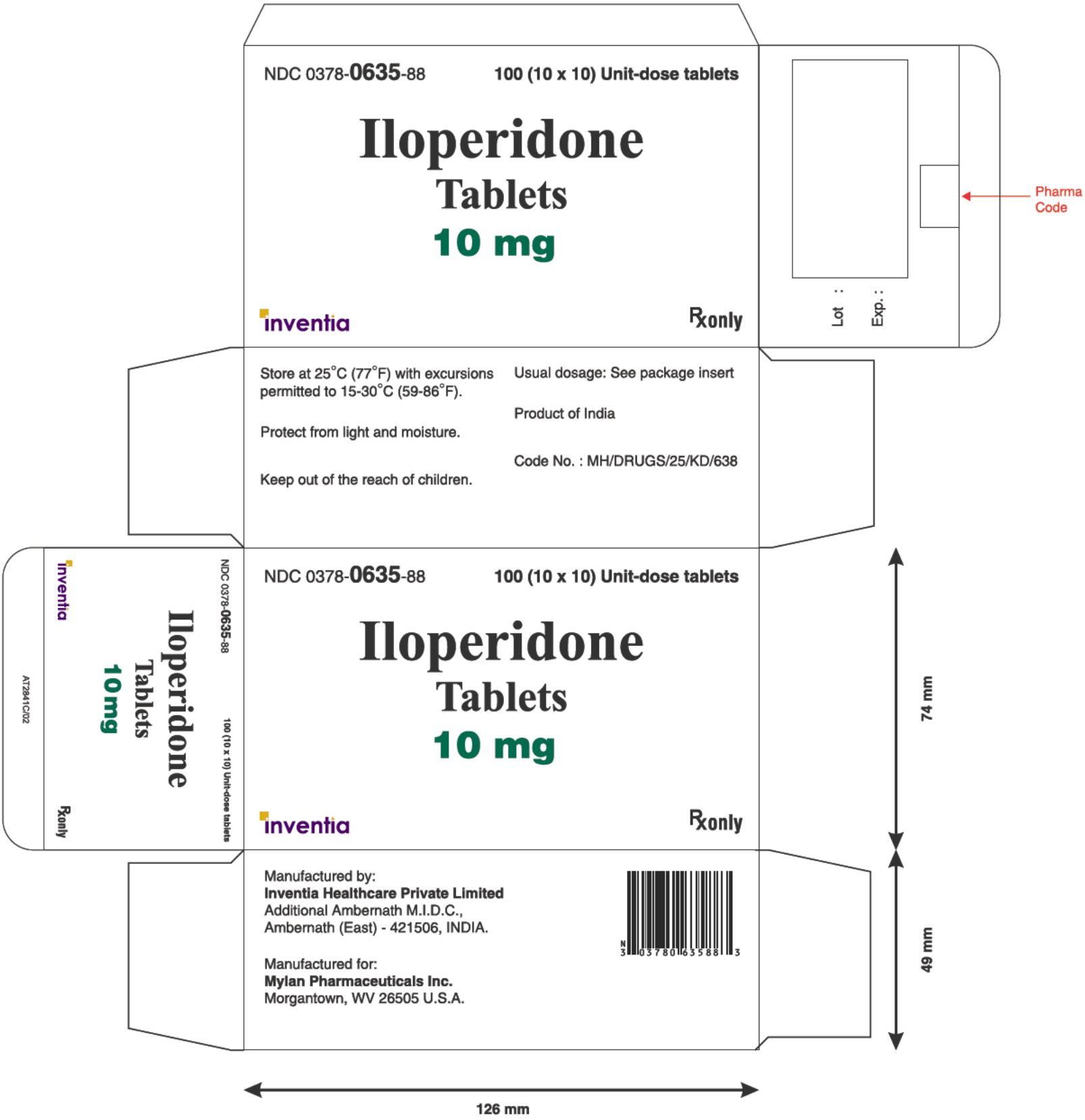

Code No MH/D RUSS/25/KD/938
AT 2840 T/01
Iloperidone
Tablet
8 mg
Lot
Exp
Product of India
inventia
120 mm
70 mm

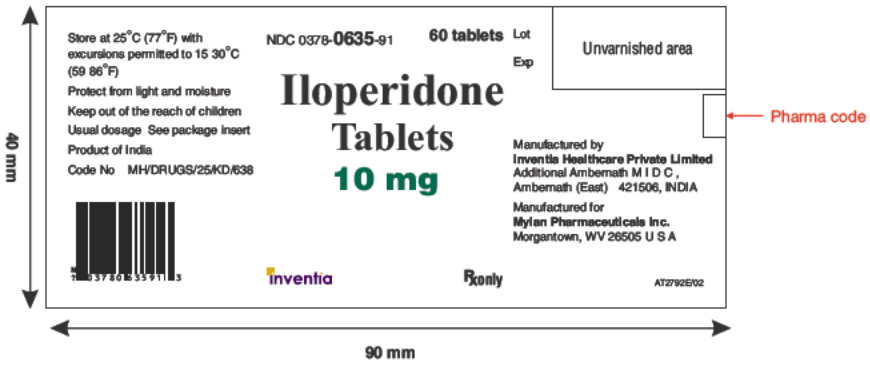

NDC 0378-0634-88
100 (10 x 10) Unit-dose tablets
Iloperidone
Tablets
8 mg
inventia
Rxonly
Lot :
Exp. :
Pharma Code
Store at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).
Protect from light and moisture.
Keep out of the reach of children.
Usual dosage: See package insert
Product of India
Code No. : MH/DRUGS/25/KD/638
NDC 0378-0634-88
100 (10 x 10) Unit-dose tablets
Iloperidone
Tablets
8 mg
inventia
Rxonly
AT2840C/02
Manufactured by:
Inventia Healthcare Private Limited
Additional Ambernath M.I.D.C.,
Ambernath (East) - 421506, INDIA.
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
74 mm
49 mm
126 mm

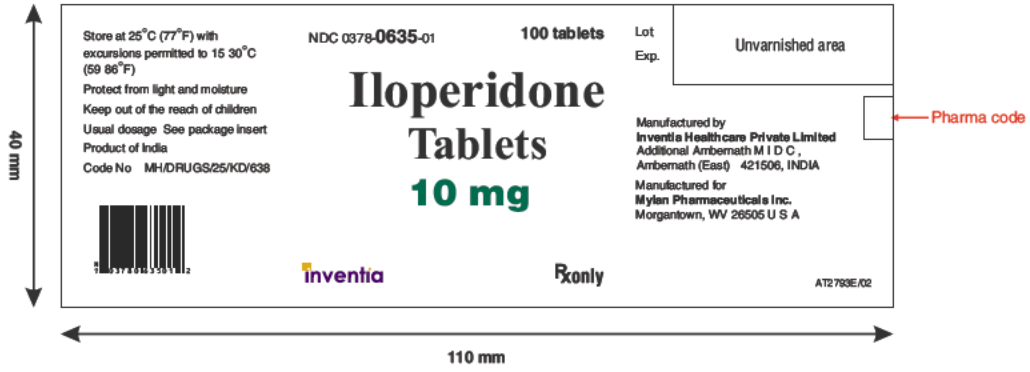

Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0634-91
60 tablets
Lot
Exp
Unvarnished area
Pharma code
Iloperidone
Tablets
8 mg
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2790E/02
40 mm
90 mm

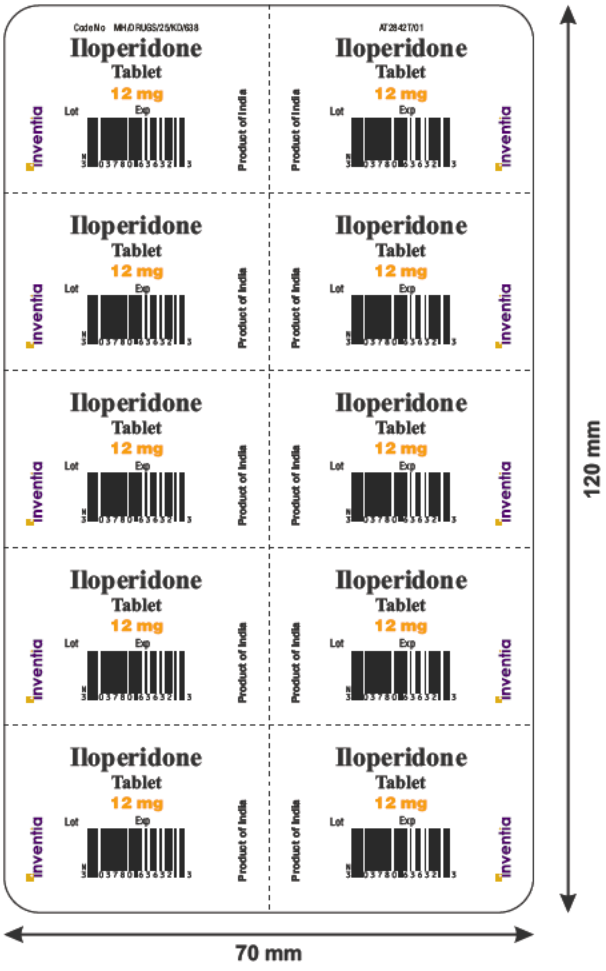

Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0634-01
100 tablets
Lot
Exp
Unvarnished area
Pharma code
Iloperidone
Tablets
8 mg
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2791E/02
40 mm
90 mm

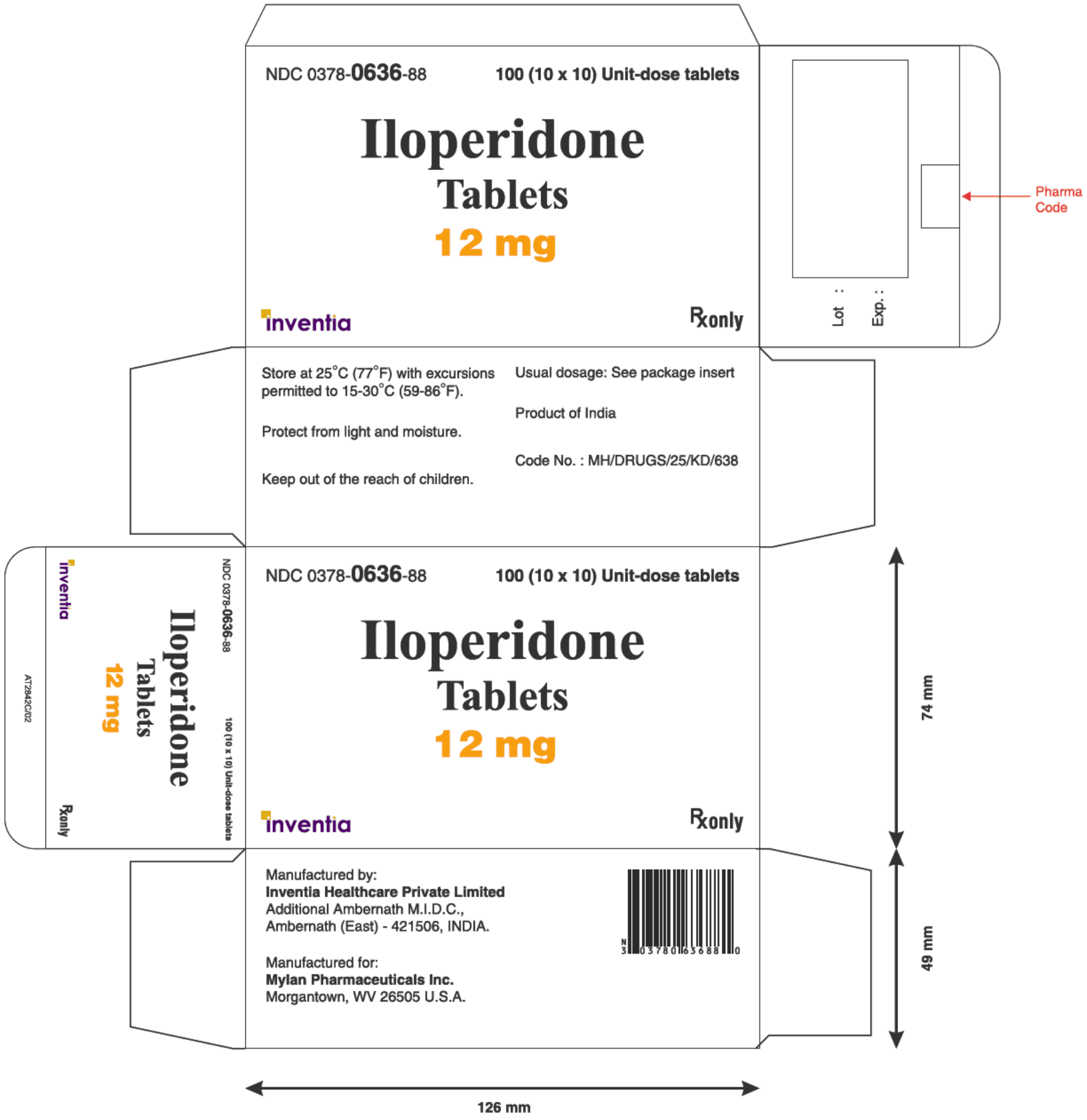

Code No MHJ/RUSS/25/KD/638
AT2841T01
Iloperidone
Tablet
10 mg
Lot
Exp
Product of India
inventia
120 mm
70 mm

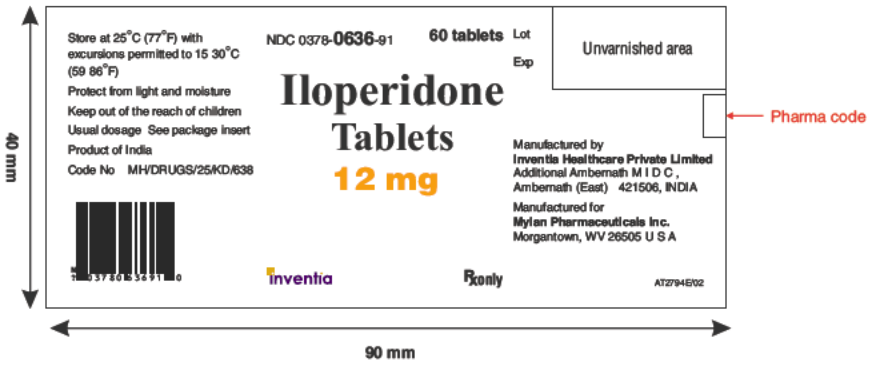

NDC 0378-0635-88
100 (10 x 10) Unit-dose tablets
Iloperidone
Tablets
10 mg
inventia
Rxonly
Lot :
Exp. :
Pharma Code
Store at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).
Protect from light and moisture.
Keep out of the reach of children.
Usual dosage: See package insert
Product of India
Code No. : MH/DRUGS/25/KD/638
Manufactured by:
Inventia Healthcare Private Limited
Additional Ambernath M.I.D.C.,
Ambernath (East) - 421506, INDIA.
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
AT2841C/02
74 mm
49 mm
126 mm

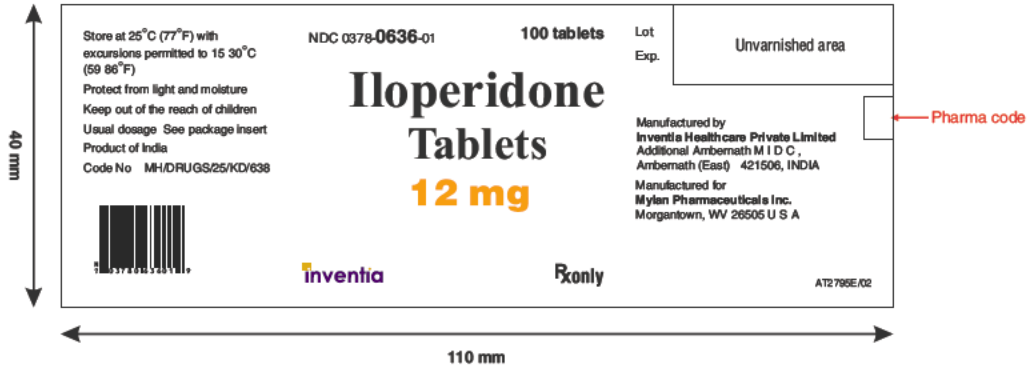

Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0635-91
60 tablets
Lot
Exp
Unvarnished area
Pharma code
Iloperidone
Tablets
10 mg
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2792E/02
40 mm
90 mm


40 mm
Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0635-01
100 tablets
Iloperidone Tablets
10 mg
inventia
Rxonly
Lot
Exp.
Unvarnished area
Pharma code
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
AT2793E/02
110 mm


Code No MHJDRUSS/25/KD/638
AT2642701
Iloperidone
Tablet
12 mg
Lot
Exp
inventia
Product of India
120 mm
70 mm


NDC 0378-0636-88
100 (10 x 10) Unit-dose tablets
Iloperidone
Tablets
12 mg
inventia
Rxonly
Pharma Code
Lot :
Exp. :
Store at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).
Protect from light and moisture.
Keep out of the reach of children.
Usual dosage: See package insert
Product of India
Code No. : MH/DRUGS/25/KD/638
AT2842C/02
74 mm
49 mm
Manufactured by:
Inventia Healthcare Private Limited
Additional Ambernath M.I.D.C.,
Ambernath (East) - 421506, INDIA.
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
126 mm


Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0636-91
60 tablets
Lot
Exp
Unvarnished area
Pharma code
Iloperidone
Tablets
12 mg
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
inventia
Rx only
AT2794E/02
40 mm
90 mm


40 mm
Store at 25°C (77°F) with excursions permitted to 15 30°C (59 86°F)
Protect from light and moisture
Keep out of the reach of children
Usual dosage See package insert
Product of India
Code No MH/DRUGS/25/KD/638
NDC 0378-0636-01
100 tablets
Iloperidone
Tablets
12 mg
inventia
Rxonly
Lot
Exp.
Unvarnished area
Pharma code
Manufactured by
Inventia Healthcare Private Limited
Additional Ambernath M I D C ,
Ambernath (East) 421506, INDIA
Manufactured for
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U S A
AT2795E/02
110 mm

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207231

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE
DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	207231
Drug Product Name	Iloperidone Tablets
Strength (s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg
Applicant Name	Inventia Healthcare Private Limited
Applicant Address	Unit 703 and 704, 7th floor Hubtown solaris N.S.Phadke Marg, Andheri (East) Mumbai, Maharashtra, India 400069
US Agent Name and the mailing address	Jeanne Taborsky SciRegs Interntional, Inc. 6333 Summercrest Drive Columbia, MD 21045
US Agent's Telephone Number	410-309-3145
US Agent's Fax Number	410-309-6145
Original Submission Date(s)	May 21, 2014
Submission Date(s) of Amendment(s) Under Review	June 10, 2015 - Bioequivalence/Response to Information Request (Dissolution Acknowledgement)
Reviewer	Mignon Schley-Lagoke, Pharm.D.
OVERALL DISSOLUTION REVIEW RESULT	**ADEQUATE**

EXECUTIVE SUMMARY

This is a review of the dissolution method and/or specification acknowledgement from Inventia Healthcare Private Limited on June 10, 2015. Inventia Healthcare Private Limited has accepted the following FDA-recommended dissolution method and specification:

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

RECOMMENDATIONS

From a bioequivalence point of view, Inventia Healthcare Private Limited 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.

DISSOLUTION COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 207231

APPLICANT: Inventia Healthcare Private Limited

DRUG PRODUCT: Iloperidone Tablets1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

The Division of Bioequivalence I (DBI) 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:	37ºC ± 0.5ºC
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}

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

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	207231
Drug Product Name	Iloperidone Tablets
Strength (s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg
Applicant Name	Inventia Healthcare Private Limited
Applicant Address	Unit 703 and 704, 7th floor Hubtown solaris N.S.Phadke Marg, Andheri (East) Mumbai, Maharashtra, India 400069
US Agent Name and the mailing address	SciRegs International, Inc. Jeanne Taborsky 6333 Summercrest Drive Columbia, MD 21045
US Agent's Telephone Number	410-309-3145
US Agent's Fax Number	410-309-6145
Original Submission Date(s)	05/21/2014
Submission Date(s) of Amendment(s) Under Review	04/02/2015
Reviewer	Susan L Young
Dissolution Method	**ADEQUATE**
OVERALL REVIEW RESULT	**INADEQUATE**

I. EXECUTIVE SUMMARY

This is a review of dissolution testing only.

The application references Fanapt (iloperidone) Tablets, 1mg, 2mg, 4mg, 6mg, 8mg, 10mg, 12mg (NDA # N022192 currently held by Vanda Pharmaceuticals, Inc and approved May 6, 2009).

There is no USP monograph for this product but there is an FDA- recommended method: 500 mL 0.1N HCl using USP apparatus II (paddle) at 50 rpm. Recommended sampling times are 5, 10, 15, 30, 45 and 60 minutes. The firm only performed the 5 minute sampling for the pilot studies, but not for the exhibit batches. For the dosage strengths 6 mg, 8 mg, 10 mg, 12 mg manufactured from a common granule lot, there is a slightly slower drug release than for the dosage strengths 1 mg, 2 mg, 4 mg. The firm's dissolution testing data utilizing the recommended method are acceptable.

The firm's proposed specification of 'Not less than (NLT) (b)(4)% (Q) of the labeled amount of iloperidone is dissolved in 30 minutes' is too liberal. Based on the data submitted, the DB recommends a more appropriate specification of NLT (b)(4)% (Q) of the labeled amount of iloperidone is dissolved in 30 minutes.

The firm's dissolution method is **inadequate**.

The fasting and fed BE studies and waiver requests will be reviewed at a later date.

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 (if any)[1]

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
iloperidone	tablet	II (Paddle)	50	0.1N HCl	500	5, 10, 15, 30, 45 and 60	08/05/2010

DB Internal Dissolution Database

NA

II.3 USP Method (if any)

NA

[1] External dissolution database: http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm, Last accessed date 4/8/2015

II.4 Summary of In Vitro Dissolution Data

Table 5 Summary of In Vitro Dissolution Studies

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	For 30 mins - Not Less Than (b)(4)% (Q)	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiry Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (mins)**					**Study Report Location**
						10	**15**	**30**	**45**	**60**	
EXB/618/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg date: Jul. 2013	1 mg Tablet	12	Mean	96	97	97	97	98	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.4	2.4	3.2	3.4	3.3	
Lot No. FFZN	Nov. 2013	Reference Listed Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	1 mg Tablet	12	Mean	93	94	95	95	95	Section 2.7.1.2
					Range	(b) (4)					
					% CV	3.0	1.9	1.8	1.8	1.6	

Table 5 Summary of In Vitro Dissolution Studies

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	For 30 mins - Not Less Than (b)(4)% (Q)	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiry Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (mins)**					**Study Report Location**
						10	**15**	**30**	**45**	**60**	
EXB/619/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg date: Jul. 2013	2 mg Tablet	12	Mean	99	100	101	102	102	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.0	1.4	2.5	2.4	2.6	
Lot No. FFZP	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	2 mg Tablet	12	Mean	94	96	96	97	97	Section 2.7.1.2
					Range	(b) (4)					
					% CV	5.0	3.5	5.0	5.3	4.4	

Table 5 Summary of In Vitro Dissolution Studies

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	For 30 mins - Not Less Than (b) (4)% (Q)	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiry Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (mins)**					**Study Report Location**
						10	**15**	**30**	**45**	**60**	
EXB/620/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg date: Jul. 2013	4 mg Tablet	12	Mean	89	93	97	97	97	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.2	1.9	2.1	2.0	1.7	
Lot No. FFZM	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	4 mg Tablet	12	Mean	92	94	97	97	97	Section 2.7.1.2
					Range	(b) (4)					
					% CV	3.6	2.4	2.3	2.0	2.7	

Table 5 Summary of In Vitro Dissolution Studies

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	For 30 mins - Not Less Than (b) (4)% (Q)	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiry Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (mins)**					**Study Report Location**
						10	**15**	**30**	**45**	**60**	
EXB/621/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg date: Jul. 2013	6 mg Tablet	12	Mean	82	91	98	99	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	3.5	2.3	2.3	2.2	2.3	
Lot No. FYPB	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Jul. 2014	6 mg Tablet	12	Mean	95	97	100	100	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	1.6	1.3	1.2	1.1	1.2	

Table 5 Summary of In Vitro Dissolution Studies

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	For 30 mins - Not Less Than (b) (4)% (Q)	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiry Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (mins)**					**Study Report Location**
						10	**15**	**30**	**45**	**60**	
EXB/622/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg date: Jul. 2013	8 mg Tablet	12	Mean	81	89	98	99	99	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.6	2.0	1.9	1.2	1.5	
Lot No. FYPC	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	8 mg Tablet	12	Mean	95	98	100	100	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	1.0	1.2	0.7	1.2	1.2	

Table 5 Summary of In Vitro Dissolution Studies

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	For 30 mins - Not Less Than (b)(4)% (Q)	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiry Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (mins)**					**Study Report Location**
						10	**15**	**30**	**45**	**60**	
EXB/623/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg date: Jul. 2013	10 mg Tablet	12	Mean	80	89	98	100	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.3	1.9	2.0	1.9	1.7	
Lot No. DXFY	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	10 mg Tablet	12	Mean	87	92	96	97	98	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.5	1.3	1.0	0.7	1.0	

Table 5 Summary of In Vitro Dissolution Studies

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	For 30 mins - Not Less Than (b)(4)% (Q)	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiry Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (mins)**					**Study Report Location**
						10	**15**	**30**	**45**	**60**	
EXB/624/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg date: Jul. 2013	12 mg Tablet	12	Mean	82	89	98	100	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	4.4	2.5	2.8	2.5	2.8	
Lot No. KKTF	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Dec. 2015	12 mg Tablet	12	Mean	92	96	100	101	101	Section 2.7.1.2
					Range	(b) (4)					
					% CV	1.5	1.7	1.6	1.2	1.4	

Dissolution Method SOP effective at the time of testing (Yes/No)	Yes, method & validation done concurrently
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.	4 months
Was the reference product expired at the time of dissolution testing (Yes/No)	No
Comments on the variability of the dissolution data	acceptable
For two-stage dissolution testing, comment on the method of medium change from acid stage to buffer stage.	NA

III. Reviewer's Comments for Dissolution Testing

- The application references Fanapt (iloperidone) tablets, 1mg, 2mg, 4mg, 6mg, 8mg, 10mg, 12mg (NDA # N022192 currently held by Vanda Pharmaceuticals, Inc and approved May 6, 2009).

- There is no USP monograph for this product but there is an FDA-recommended method: 500mL 0.1N HCl using USP apparatus II (paddle) at 50 rpm. Recommended sampling times are 5, 10, 15, 30, 45 and 60 minutes. The firm only performed the 5 minute sampling for the pilot studies, but not for the exhibit batches. For the dosage strengths 6 mg, 8 mg, 10 mg, 12 mg manufactured from a common granule lot, there is a slightly slower drug release than for the dosage strengths 1 mg, 2 mg, 4 mg. The firm's dissolution testing data utilizing the recommended method are acceptable.

- The firm's proposed specification 'Not less than (b)(4)% (Q) of the labeled amount of iloperidone is dissolved in 30 minutes' is too liberal. Based on the data submitted, the DB recommends specification of NLT (b)(4)% (Q) of the labeled amount of iloperidone is dissolved in 30 minutes.

- The DB recommended specification 'NLT (b)(4)% (Q) in 30 minutes' is the same as recommended by the NDA applicant for the RLD product. The reviewer checked the NDA Annual report for the above mentioned specification for the RLD product.

- The firm's dissolution method is **inadequate.**

IV. Deficiency Comments for Dissolution Testing

The firm's proposed specification is:

Not less than (b)(4)% (Q) of the labeled amount of iloperidone is dissolved in 30 minutes. Based on the data submitted, the firm's specification is too liberal. The firm should acknowledge the FDA recommended specification of NLT (b)(4)% (Q) of the labeled amount of iloperidone is dissolved in 30 minutes.

V. Dissolution Recommendations

The in vitro dissolution conducted by Inventia Healthcare Private Limited on its test product Iloperidone Tablets, 1 mg (batch # EXB/618/01 manufactured July 2013), 2 mg (batch # EXB/619/01 manufactured July 2013), 4 mg (batch # EXB/620/01 manufactured July 2013), 6 mg (batch # EXB/621/01 manufactured July 2013), 8 mg (batch # EXB/622/01 manufactured July 2013), 10 mg (batch # EXB/623/01 manufactured July 2013), 12 mg (batch # EXB/624/01 manufactured July 2013), comparing them to Fanapt (iloperidone) Tablets, 1 mg (batch # FFZN expiration April 2014), 2 mg (batch # FFZP expiration April 2014), 4 mg (batch # FFZM expiration April 2014), 6 mg (batch # FYPB expiration July 2014), 8 mg (batch # FYPC expiration April 2014), 10 mg (batch # DXFY expiration April 2014), 12 mg (batch # KKTF expiration December 2015), is **inadequate** due to the deficiency comment above**.**

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT
(PROCESSED BY BIO-PM)

ANDA: 207231

APPLICANT: Inventia Healthcare Private Limited

DRUG PRODUCT: Iloperidone Tablets1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

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

Your dissolution testing data are acceptable; however, your proposed specification is too liberal and not acceptable. Please acknowledge the following FDA recommended method and specification for your test product:

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

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 REVIEW

ANDA No.	207231	
Drug Product Name	Iloperidone Tablets	
Strength(s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg	
Applicant Name	Inventia Healthcare Private Limited	
Applicant Address	Unit 703 and 704, 7th floor, Hubtown solaris, N.S.Phadke Marg, Andheri(East), Mumbai, Maharashtra, India, 400069 prasad.virkar@inventiahealthcare.com	
US Contact Name and US Mailing Address	C. Jeanne Taborsky, President and CEO, SciRegs International, Inc., US Agent 6333 Summercrest Drive, Columbia, MD, 21045 jeanne.taborsky@SciRegs.com	
US Contact Telephone Number	410-309-3145	
US Contact Fax Number	410-309-6145	
Original Submission Date(s)	05/21/2014	
Submission Date(s) of Amendment(s) Under Review	N/A	
Reviewer	Yi Zhang, M.D., Ph.D.	
Study Number(s)	H216-12	H217-12
Study Type(s)	Fasting	Fed
Strength(s)	2 x 1 mg	2 x 1 mg
Clinical Site	Clinical Pharmacology Unit GVK BIOSCIENCES PVT. LTD.	
Clinical Site Address	1st& 7th Floor, Swarna Jayanthi Commercial Complex Ameerpet, Hyderabad – 500 038, India. Phone No.: +91-40-6627-5555 Fax No.: +91-40-6627-5599	
Analytical Site	(b) (4)	
Analytical Site Address		
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete** ☐ **N/A (Waiver)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**

Waiver	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A		
QC Dissolution	☐ Pending ☒ Adequate ☐ Inadequate		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A		
Overall Review Result	☒ Adequate ☐ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Communication	☐ ECD ☐ IR ☒ Not Applicable		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	**Fasting**	**1 mg**	☒ Adequate ☐ Inadequate
1	**Fed**	**1 mg**	☒ Adequate ☐ Inadequate
1	**Waiver**	**2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg**	☒ Adequate ☐ Inadequate

1 EXECUTIVE SUMMARY

This application contains the results of the fasting and fed bioequivalence (BE) studies comparing a test product, Inventia Healthcare Private Limited's Iloperidone Tablets, 1 mg to the corresponding reference product Fanapt® (iloperidone) tablets, 1 mg. 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.

Iloperidone Tablets (No of subjects completed = 46) Dose (2 × 1 mg) Iloperidone Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study No. H216-12						
Parameter (units)	**N**	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	46	21521.24	21198.30	1.02	98.09	105.08
AUC∞ (hr *pg/ml)	46	23742.49	23252.46	1.02	98.13	106.24
Cmax (pg/ml)	46	1298.86	1307.87	0.99	89.73	109.92

Iloperidone Tablets (No of subjects completed = 46) Dose (2 × 1 mg) P88 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study No. H216-12						
Parameter (units)	**N**	**Test**	**RLD**	**Ratio**		
AUC0-t (hr *pg/ml)	46	47740.49	47181.02	1.01		
AUC∞ (hr *pg/ml)	46	54400.06	54358.11	1.00		
Cmax (pg/ml)	46	1834.23	1767.49	1.04		

Iloperidone Tablets (No of subjects completed = 66) Dose (2 × 1 mg) Iloperidone Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study No. H217-12						
Parameter (units)	**N**	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	66	24319.62	24641.24	0.99	96.55	100.89
AUC∞ (hr *pg/ml)	66	26260.64	26748.58	0.98	95.87	100.54
Cmax (pg/ml)	66	1235.14	1322.78	0.93	87.69	99.43

Iloperidone Tablets (No of subjects completed = 66) Dose (2 × 1 mg) P88 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study No. H217-12						
Parameter (units)	**N**	**Test**	**RLD**	**Ratio**		
AUC0-t (hr *pg/ml)	66	63956.49	65265.35	0.98		
AUC∞ (hr *pg/ml)	66	73285.47	74597.09	0.98		
Cmax (pg/ml)	66	2058.48	2133.44	0.96		

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

In addition to the pivotal BE studies, the firm conducted three pilot studies: pilot fasting (H029-12), pilot fed (H030-12), and pilot fasting (H031-12) in healthy subjects. The formulations of studies# H029-12 and H030-12 are similar to the formulation of the pivotal BE studies; the formulation of study H031-12 are identical to the formulation of the pivotal BE studies. For all three pilot BE studies, the 90% CI for Cmax falls outside the acceptable BE limit of 80-125%, therefore were failed to demonstrate bioequivalence.

All studies were considered to be underpowered as the numbers of subjects enrolled in the studies were inadequate (N ≤ 11).

Dissolution data were reviewed separately, and the firm's in vitro dissolution testing with the FDA-recommended method and specification is **adequate**[1]. The dissolution data are adequate with respect to supporting waiver requests of the lower strengths.

The Division of bioequivalence (DB) **grants the waiver** of in vivo bioequivalence study requirements for the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 m strengths of the test product, Iloperidone Tablets, under the Section 21 CFR § 320.22 (d) (2).

No Office of Study Integrity and Surveillance (OSIS) inspection is pending or necessary.

The application is acceptable with no deficiencies.

[1] GDRP ANDA-207206-ORIG-1, Biopharmaceutics Primary Review (completion date 13-Mar-2015), http://panorama fda.gov/project/view?ID=542105b400174cbeecd761dc1a9f65e4

2 TABLE OF CONTENTS

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[2]	Fanapt® (iloperidone) Tablets, 1 mg (RLD), 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg
RLD Manufacturer	Vanda Pharmaceuticals Inc.
NDA No.	22192
RLD Approval Date	May 6, 2009 (all 7 strengths)

3.2 PK/PD Information[3]

Most recent RLD label (provide embedded document)	RLD labeling_022192.pdf
Indication	Fanapt® is an atypical antipsychotic agent and indicated for the treatment of schizophrenia in adults. Efficacy was established in two short-term (4-and 6-week) placebo-and active-controlled studies of adult patients with schizophrenia. In choosing among treatments, prescribers should consider the ability of Fanapt® to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate Fanapt® slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration.
Boxed warning	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)

[2] Electronic Orange Book (Updated Through January 2016): last assessed: 02/29/2016. http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=022192&TABLE1=OB_Rx

[3] RLD label (DRUGS@FDA;Initial U.S. Approval: 2009, last revised 01/05/2016, last accessed 2/26/2016, http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022192s017lbl.pdf

	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. FANAPT is not approved for the treatment of patients with Dementia-Related Psychosis.
Bioavailability	Iloperidone is well absorbed after administration of the tablet. 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 Cmax or AUC of iloperidone, P88, or P95, but delayed Tmax by 1 hour for iloperidone, 2 hours for P88 and 6 hours for P95. FANAPT can be administered without regard to meals.
Tmax	Within 2 to 4 hours
Metabolism	Elimination of iloperidone is mainly through hepatic metabolism involving 2 P450 isozymes, CYP2D6 and CYP3A4. 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 ultra-rapid metabolizers. Coadministration of FANAPT 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 FANAPT 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. Iloperidone and P88 are not substrates of P-gp and iloperidone is a weak P-gp inhibitor.
Excretion	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. Steady-state concentrations are attained within 3-4 days of dosing.
Maximum Daily Dose	24 mg

3.3 OGD Recommendations for Drug Product

<table>
<tr><td>Source of most recent recommendations or provide the embedded document to the current draft guidance</td><td colspan="2"> 
Draft Guidance on Iloperidone 2010.pdf</td></tr>
<tr><td rowspan="4">Summary of OGD or DB History</td><td>Approved ANDAs:</td><td>None (as per Electronic Orange Book search as of 02/29/2016)</td></tr>
<tr><td>Pending ANDAs</td><td>
<table>
<tr><th>ANDA #</th><th>Firm</th><th>Pending Date</th></tr>
<tr><td>(b) (4)</td><td></td><td></td></tr>
<tr><td>207231</td><td>Inventia (Current)</td><td>05/21/2014</td></tr>
<tr><td>206890</td><td>Lupin</td><td>02/16/2016</td></tr>
</table>
Three ANDAs received Complete Response:
<table>
<tr><th>ANDA #</th><th>Firm</th><th>Status Date</th></tr>
<tr><td>207409</td><td>ALEMBIC</td><td>09/22/2015</td></tr>
<tr><td>207098</td><td>TARO</td><td>10/26/2015</td></tr>
</table>
(b) (4)
(b) (4)</td></tr>
<tr><td>Protocols [5]</td><td>None</td></tr>
<tr><td>Pending Citizen Petitions and other legal and</td><td>☐ Yes ☒ No</td></tr>
</table>

[4] OGD Controls (Correspondence) Document Tracking http://cdsogd1/controls/DOC.ASP, search for 'iloperidone', last accessed 2/26/2016

[5] OGD - Division of Bioequivalence Protocols Tracking http://fdswv04385/seltrack/Protocols.asp, search for 'iloperidone', last accessed 2/29/2016

	regulatory issues:[6] If yes, please comment.	

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte: Iloperidone	
Bioanalytical method validation report location	**Module 5.3.1.4, page 158 of 1493**	
Analyte	Iloperidone	
Internal standard (IS)	Iloperidone D3	
Method description	Liquid chromatographic method using mass detector with Liquid-Liquid Extraction	
Limit of quantitation	19.796 pg/mL	
Recovery of drug at each QC (%CV)	85.2% HQC: 82.4% (6.3%) MQC: 85.1% (3.4%) LQC: 88.1% (3.2%)	
Average recovery of IS (%)	91.5% (4.3%)	
Standard curve concentrations (pg/mL)	19.796 to 5022.510 pg/mL	
QC concentrations (pg/mL)	HQC - 4295.653 pg/mL MQC - 2147.826 pg/mL LQC - 56.917 pg/mL LOQ QC - 19.921 pg/mL	
	HQC, MQC, LQC	**LOQ QC**
QC Intraday precision range (%)	1.9% - 5.0%	9.7%
QC Intraday accuracy range (%)	95.3% - 99.4%	101.8%
QC Interday precision range (%)	3.4% - 5.1%	12.6%
QC Interday accuracy range (%)	94.0% - 96.4%	99.8%
Extended P&A precision	2.3% - 5.7%	13.5%
Extended P&A accuracy	96.5% - 97.9%	112.0%
Reinjection reproducibility precision	1.7% - 3.9%	5.8%
Reinjection reproducibility accuracy	94.4% - 96.9%	97.1%
Reinjection reproducibility	35 hours 49 minutes	
Bench-top stability (hrs)	06 hours 37 minutes at 24 ± 4°C	
Short term stock solution stability	Iloperidone– 06Hours 54 Minutes at 24 ± 4°C Iloperidone d_3 – 07 Hours 22 Minutes at 24 ± 4°C Iloperidone d_3 Dilution – 07 Hours 44 Minutes at 24±4°C	
Long term stock solution stability	Iloperidone – 79 days at 2-8°C Iloperidone d3 – 79 days at 2-8°C	

[6] DLRS policy updates, OGD Policy Alert List as of 02/26/2016, http://sharepoint fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx

Intermediate term stability	05 days 15 hours 36 minutes at -20 ± 10° C
Processed stability	Post extract stability - 09 hours 05 minutes at 24 ± 4°C
	Dry extract stability – 33 hours 07 minutes at 2 – 8°C
	Autosampler stability - 04 days 14 hours 05 minutes at 10 ± 1°C
Calibration curve stability	05 days 15 hours 25 minutes at -70 ± 20° C
Freeze-thaw stability	FT – VI Cycles
Long term matrix storage stability (days)	77 days at -70 ± 20° C
Whole blood stability	02 hours 20 minutes at 24 ± 4°C
Dilution integrity	1/2nd - Precision – 2.1% 1/2nd - Accuracy – 100.9% 1/5th - Precision – 0.5% 1/5th - Accuracy – 106.9%
Matrix effect (ISTD normalized matrix factor)	Precision HQC – 1.0% Precision LQC – 2.7%
Selectivity and Specificity	No significant Interference was observed at the retention time of Analyte and ISTD with respect to aqueous and extracted LOQ.
Auto sampler carry over test	Carry over was not observed for Iloperidone and Iloperidone D3 with respect to aqueous and extracted samples.

Information Requested	**Analyte: Metabolite P88**	
Bioanalytical method validation report location	**Module 5.3.1.4, page 159 of 1493**	
Analyte	Iloperidone Metabolite P88	
Internal standard (IS)	Iloperidone D3 Metabolite P88	
Method description	Liquid chromatographic method using mass detector with Liquid-Liquid Extraction	
Limit of quantitation	19.786 pg/mL	
Recovery of drug at each QC (%CV)	89.4% HQC: 83.4% (7.5%) MQC: 91.1 % (4.1%) LQC: 93.7% (3.7%)	
Average recovery of IS (%)	94.6% (5.3%)	
Standard curve concentrations (pg/mL)	19.786 to 5019.930 pg/mL	
QC concentrations (pg/mL)	HQC - 4294.937 pg/mL MQC - 2147.469 pg/mL LQC - 56.908 pg/mL LOQ QC - 19.918 pg/mL	
	HQC, MQC, LQC	**LOQ QC**
QC Intraday precision range (%)	1.9% - 3.6%	5.0%
QC Intraday accuracy range (%)	95.2% - 99.4%	103.9%
QC Interday precision range (%)	4.0% - 4.6%	6.4%

QC Interday accuracy range (%)	92.4% - 95.5%	98.0%
Extended P&A precision	2.1% -3.5%	5.0%
Extended P&A accuracy	94.4% - 97.2%	103.5%
Reinjection reproducibility precision	1.0% - 2.9%	3.1%
Reinjection reproducibility accuracy	93.2% - 97.1%	97.4%
Reinjection reproducibility	35 hours 49 minutes	
Bench-top stability (hrs)	06 hours 37 minutes at 24 ± 4°C	
Short term stock solution stability	Iloperidone Metabolite P88– 07 hours 06 minutes at 24 ± 4°C Iloperidone D3 Metabolite P88– 07 hours 30 minutes at 24 ± 4°C Iloperidone D3 Metabolite P88 Dilution – 07 hours 44 minutes at 24 ± 4°C	
Long term stock solution stability	Iloperidone Metabolite P88– 79 days at 2-8°C Iloperidone D3 Metabolite P88 – 79 days at 2-8°C	
Intermediate term stability	05 days 15 hours 36 minutes at -20 ± 10° C	
Processed stability	Post extract stability - 09 hours 05 minutes at 24 ± 4°C	
	Dry extract stability – 33 hours 07 minutes at 2 – 8°C	
	Autosampler stability - 04 days 14 hours 05 minutes at 10 ± 1°C	
Calibration curve stability	05 days 15 hours 25 minutes at -70 ± 20° C	
Freeze-thaw stability	FT – VI Cycles	
Long term matrix storage stability (days)	77 days at -70 ± 20° C	
Whole blood stability	03 hours 25 minutes at 24 ± 4°C	
Dilution integrity	(b) (4) [redacted]	
Matrix effect (ISTD normalized matrix factor)	Precision HQC – 1.2% Precision LQC – 2.3%	
Selectivity and Specificity	No significant Interference was observed at the retention time of Analyte and ISTD with respect to aqueous and extracted LOQ.	
Auto sampler carry over test	Carry over was not observed for Iloperidone Metabolite P88 and Iloperidone D3 Metabolite P88 with respect to aqueous and extracted samples.	

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes ☐ No K_2EDTA was used.
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No

Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation: Adequate

3.5 In Vivo Studies

Iloperidone

Iloperidone											
Study Ref. No.	**Study Objective**	**Study Design**	**Treatments (Dose, Dosage Form, Route) [Product ID]**	**Subjects No. (M/F) Type Age: mean (Range)**	***Mean Parameters ± SD (%CV)**						**Study Report Location**
					C_{max} (pg/mL)	**T_{max} (hr)**	**AUC_{0-t} (pg*h/mL)**	**$AUC_{0-\infty}$ (pg*h/mL)**	**T½ (hr)**	**K_{el} (hr-1)**	
H216-12	To determine the single-dose oral BE of Iloperidone Tablets (2x1 mg) of Inventia Healthcare Pvt Ltd., India and Fanapt® iloperidone tablets (2x1 mg) Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 in normal, healthy, adult, human subjects under **fasting** condition.	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover, pivotal oral BE study in normal, healthy, adult, human subjects under **fasting** condition	**Test Product-T:** Dose: 2x1 mg Iloperidone Tablets 1 mg Batch No: EXB/618/01 Route: Oral	Participated Subjects: 52 Mean age: 26.4 (18-39) Clinical Phase Completed Subjects: 46 Mean age: 26.3 (18-39)	1454.005 ± 717.6113 (49.4)	2.00 (1.00-8.00)	24314.631 ± 15188.1757 (62.5)	26828.039 ± 17120.8854 (63.8)	39.16 ± 27.265 (69.6)	0.0218 ± 0.00735 (33.8)	5.3.1.2 Study Report
			Reference Product-R: Dose: 2x1 mg Fanapt® iloperidone tablets 1 mg Lot No.: FFZN Route: Oral		1435.642 ± 604.2334 (42.1)	2.00 (1.00-5.00)	23812.828 ± 14329.3961 (60.2)	26240.686 ± 16268.1304 (62.0)	36.20 ± 17.192 (47.5)	0.0217 ± 0.00626 (28.9)	

Iloperidone											
Study Ref. No.	**Study Objective**	**Study Design**	**Treatments (Dose, Dosage Form, Route) [Product ID]**	**Subjects No. (M/F) Type Age: mean (Range)**	***Mean Parameters ± SD (%CV)**						**Study Report Location**
					C_{max} (pg/mL)	**T_{max} (hr)**	**AUC_{0-t} (pg*h/mL)**	**$AUC_{0-\infty}$ (pg*h/mL)**	**T½ (hr)**	**K_{el} (hr-1)**	
H217-12	To determine the single-dose oral BE of Iloperidone Tablets (2x1 mg) of Inventia Healthcare Pvt Ltd., India and Fanapt® iloperidone tablets (2x1 mg) Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 in normal, healthy, adult, human subjects under **fed** condition.	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover, pivotal oral BE study in normal, healthy, adult, human subjects under **fed** condition	**Test Product-T:** Dose: 2x1 mg Iloperidone Tablets 1 mg Batch No: EXB/618/01 Route: Oral	Participated Subjects: 72 Mean age: 26.0 (18-41) Clinical Phase Completed Subjects: 66 Mean age: 26.0 (18-41)	1334.769 ± 525.7495 (39.4)	4.50 (1.00-8.00)	25704.144 ± 8568.1268 (33.3)	27726.391 ± 9245.5463 (33.3)	33.24 ± 14.357 (43.2)	0.0232 ± 0.00647 (27.9)	5.3.1.2 Study Report
			Reference Product-R: Dose: 2x1 mg Fanapt® iloperidone tablets 1 mg Lot No.: FFZN Route: Oral		1470.085 ± 680.8210 (46.3)	3.50 (1.00-6.00)	26060.606 ± 8968.9459 (34.4)	28258.687 ± 9663.6364 (34.2)	34.35 ± 13.513 (39.3)	0.0227 ± 0.00705 (31.0)	

* Arithmetic mean ± SD (CV %) except for Tmax for which the median (range) are reported.

Active Metabolite P88

Iloperidone active P88 metabolite											
Study Ref. No.	**Study Objective**	**Study Design**	**Treatments (Dose, Dosage Form, Route) [Product ID]**	**Subjects No. (M/F) Type Age: mean (Range)**	***Mean Parameters ± SD (%CV)**						**Study Report Location**
					C_{max} (pg/mL)	**T_{max} (hr)**	**AUC_{0-t} (pg*h/mL)**	**$AUC_{0-\infty}$ (pg*h/mL)**	**T½ (hr)**	**K_{el} (hr-1)**	
H216-12	To determine the single-dose oral BE of Iloperidone Tablets (2x1 mg) of Inventia Healthcare Pvt Ltd., India and Fanapt® iloperidone tablets (2x1 mg) Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 in normal, healthy, adult, human subjects under **fasting** condition.	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover, pivotal oral BE study in normal, healthy, adult, human subjects under **fasting** condition	**Test Product-T:** Dose: 2x1 mg Iloperidone Tablets 1 mg Batch No: EXB/618/01 Route: Oral	Participated Subjects: 52 Mean age: 26.4 (18-39) Clinical Phase Completed Subjects: 46 Mean age: 26.3 (18-39)	2040.613 ± 979.4973 (48.0)	3.50 (1.00-24.00)	51272.281 ± 18174.1347 (35.4)	58157.615 ± 20049.8178 (34.5)	43.51 ± 11.605 (26.7)	0.0171 ± 0.00476 (27.9)	5.3.1.2
			Reference Product-R: Dose: 2x1 mg Fanapt® iloperidone tablets 1 mg Lot No.: FFZN Route: Oral		1971.347 ± 927.9333 (47.1)	2.50 (1.50-8.00)	50971.265 ± 18704.2567 (36.7)	58500.694 ± 21276.6667 (36.4)	47.37 ± 13.753 (29.0)	0.0159 ± 0.00520 (32.7)	

Iloperidone active P88 metabolite											
Study Ref. No.	**Study Objective**	**Study Design**	**Treatments (Dose, Dosage Form, Route) [Product ID]**	**Subjects No. (M/F) Type Age: mean (Range)**	***Mean Parameters ± SD (%CV)**						**Study Report Location**
					C_{max} (pg/mL)	**T_{max} (hr)**	**AUC_{0-t} (pg*h/mL)**	**$AUC_{0-\infty}$ (pg*h/mL)**	**T½ (hr)**	**K_{el} (hr-1)**	
H217-12	To determine the single-dose oral BE of Iloperidone Tablets (2x1 mg) of Inventia Healthcare Pvt Ltd., India and Fanapt® iloperidone tablets (2x1 mg) Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 in normal, healthy, adult, human subjects under **fed** condition.	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover, pivotal oral BE study in normal, healthy, adult, human subjects under **fed** condition	**Test Product-T:** Dose: 2x1 mg Iloperidone Tablets 1 mg Batch No: EXB/618/01 Route: Oral	Participated Subjects: 72 Mean age: 26.0 (18-41) Clinical Phase Completed Subjects: 66 Mean age: 26.0 (18-41)	2142.015 ± 621.1127 (29.0)	5.25 (1.50 – 10.00)	66668.958 ± 19274.3803 (28.9)	76375.016 ± 22072.3831 (28.9)	45.67 ± 15.007 (32.9)	0.0166 ± 0.00467 (28.2)	5.3.1.2
			Reference Product-R: Dose: 2x1 mg Fanapt® iloperidone tablets 1 mg Lot No.: FFZN Route: Oral		2205.832 ± 548.3602 (24.9)	4.50 (1.00 – 8.03)	67645.683 ± 17937.9683 (26.5)	77588.357 ± 22152.9600 (28.6)	44.96 ± 11.987 (26.7)	0.0164 ± 0.00381 (23.3)	

* Arithmetic mean ± SD (CV %) except for Tmax for which the median (range) are reported.

3.6 OSIS Status (if applicable)

A. Clinical Site

Clinical Site Name	Clinical Pharmacology Unit GVK BIOSCIENCES PVT. LTD.
Clinical Site Address	1st& 7th Floor, Swarna Jayanthi Commercial Complex Ameerpet, Hyderabad – 500 038, India.
Clinical Study Dates	10/24/2013 – 1/3/2014

Application (ANDA/NDA)	**Inspected BE Study Type (In Vivo, In Vitro)**	**Inspection Type (Routine or For Cause)**	**EIR Report Date**	**Inspection Outcome (NAI, VAI, OAI)**	**Study dates of inspected clinical studies**		**Current ANDA clinical study dates**		**Were the current ANDA clinical studies conducted within 3.5 years of the inspected clinical studies? (Yes/No)**	**Conclusion (Relevant, Irrelevant)**
					Start Date MM/DD/YY	**End Date MM/DD/YY**	**Start Date MM/DD/YY**	**End Date MM/DD/YY**		
ANDA 204901	In Vivo	Routine	1/29/2015	VAI	9/10/2011	9/22/2011	10/24/2013	1/3/2014	Yes	Relevant
ANDA 204504	In Vivo	Routine	2/4/2015	VAI	8/8/2012	8/18/2012	10/24/2013	1/3/2014	Yes	Relevant

NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated.

B. Analytical Site

Analytical Site Name	(b) (4)
Analytical Site Address	
Analytical Study Dates	

Application (ANDA/NDA)	Inspected BE Study Type (In Vivo, In Vitro)	Inspection Type (Routine or For Cause)	EIR Report Date	Inspection Outcome (NAI, VAI, OAI)	Study dates of inspected clinical studies		Current ANDA clinical study dates		Were the current ANDA clinical studies conducted within 3.5 years of the inspected clinical studies? (Yes/No)	Conclusion (Relevant, Irrelevant)
					Start Date MM/DD/YY	End Date MM/DD/YY	Start Date MM/DD/YY	End Date MM/DD/YY		
ANDA 204901	In Vivo	Routine	(b) (4)	VAI	(b) (4)					
ANDA 204504	In Vivo	Routine		VAI						

NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated.

Reviewer's Comments

The OSIS conducted routine inspections of the clinical site and the analytical site (b) (4) during (b) (4) for the clinical and analytical potions of the studies under ANDA 204901 and ANDA 204504. Following the inspection, Form FDA-483 was issued. The final classification was VAI (Voluntary Action Indicated) for both clinical and analytical sites. The inspection report was finalized at GDRP ANDA-204901-ORIG-1[7] and ANDA-204504-ORIG-1-AMEND-10[8].

Form FDA-483 study specific and general observations are provided below along with the conclusions per reviewer from Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the OSIS.

[7] GDRP ANDA-204901-ORIG-1, http://panorama fda.gov/project/view?ID=5420f38500051ce6ce04bdd6866e1df0, completion date (b) (4)
[8] GDRP ANDA-204504-ORIG-1-AMEND-10, http://panorama fda.gov/project/view?ID=5491d5550023ccc616992fce3074f7ed, completion date (b) (4)

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

Current Reviewer's Comment:

Per the DGDBE reviewer, the firms' written response to above mentioned observations 2(a), 2(b), and 3 are acceptable. The observed condition did not impact subject safety or data integrity in studies under inspection. No significant discrepancies had been found between the un-archived records and reports. The observation 1 did not directly affect the 4 studies under audit. DGDBE reviewer recommended that the data for studies under audit be accepted for further agency review.

The current reviewer agrees with the DGDBE reviewer that the nature of the FDA-483 observations may potentially affect the overall record and data integrity. The current reviewer checked the application and study data cautiously per the above OSIS recommendation. After verification of the study data, no conduct issues and data integrity deficiencies were identified by the reviewer. The reviewer considers that the observations noted for ANDA 204901 and ANDA 204504 do not impact the study outcome in the current application NDA 207231.

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	H216-12
Study Title	Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover pivotal oral bioequivalence study of Iloperidone Tablets (2x1 mg) of Inventia Healthcare Pvt Ltd., India and Fanapt® iloperidone tablets (2x1 mg) (b) (4) Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 in normal, healthy, adult, human subjects under fasting condition.
Clinical Site (Name & Address)	Clinical Pharmacology Unit GVK BIOSCIENCES PVT. LTD. 1st& 7th Floor, Swarna Jayanthi Commercial Complex Ameerpet, Hyderabad – 500 038, India. Phone No.: +91-40-6627-5555 Fax No.: +91-40-6627-5599
Principal Clinical Investigator	Dr. Ch. Nagaratnam, MD nagaratnam.chitibomma @gvkbio.co Dr. Naveen Govikar, MBBS naveen.govikar@gvkbio.com
Dosing Dates	Period 01: 16 Dec 2013 Period 02: 03 Jan 2014
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	
Principal Analytical Investigator	
Sample Storage : **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	54 days (Iloperidone) 55 days (Iloperidone Metabolite P88) –70 ± 20°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Iloperidone: 79 days @ –2 to 8°C Iloperidone Metabolite P88: 79 days @ –2 to 8°C

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	RLD
Treatment ID	T	R
Product Name	Iloperidone Tablets 1 mg	Fanapt® (iloperidone) tablets 1 mg
Manufacturer	Inventia Healthcare Pvt Ltd	(b) (4)
Distributed by	–	Novartis Pharmaceuticals Corporation East Hanover, NJ 07936
Batch/Lot No.	EXB/618/01	FFZN
Manufacture Date	Jul 2013	NAV
Expiration Date	Jun. 20I5	APR 2014
Strength	1 mg	1 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	99.7 %	97.4 %
Content Uniformity (expressed as AV per USP)	3.20	5.02
Dose Administered	1 mg x 2 tablet	1 mg x 2 tablet
Route of Administration	Oral	Oral

Are the test and reference products expired at the time of study? If Yes, please comment	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? If No, please comment	☒ Yes ☐ No
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? If No, please comment	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%? If No, please comment	☒ Yes ☐ No

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 52 (with two additional subjects (b) (6) Dosed: 52 in Period I[10], 46 in Period II[11] Completed: 46 Samples Analyzed: 46 Statistically Analyzed: 46
No. of Sequences	2 (sequence 1 TR; sequence 2 RT)
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	18 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Twenty two blood samples were collected from each subject during each period at pre-dose (0.00) and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00, 96.00 and 120.00 hours after dosing.
IRB Approval	☒ Yes Date: Protocol- approved 24 Sep 2013, Amendment No.: 01- approved 12 Dec 2013 ☐ No
Informed Consent	☒ Yes Date: Subjects willing to participate in the study underwent a screening procedure within the 28 days prior to dose administration in Period 01. Written informed consent for the screening procedure was obtained from each subject. The subjects found eligible for participation in the study underwent a study specific informed consent presentation on the day of check-in for Period 01. ☐ No
Length of Fasting	Overnight fast of at least 10 hours
Length of Confinement	In both the study periods, subjects were housed at the clinical facility from not less than 10.5 hours pre-dose till 48 hours post-dose.
Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design: Adequate

[10] Subjects No. (b) (6) withdrew consent on their accord in person prior to period I dosing, hence were replaced with Subjects (b) (6) who were later allotted Subjects No. (b) (6) respectively.
[11] Subjects No. (b) (6) were withdrawn from the study in Period I due to AEs. Subjects No. (b) (6) did not report to the facility for period II checked in.

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Fasting Bioequivalence Study No. H216-12			
		Treatment Groups	
		Test Product N = 46	Reference Product N = 46
Age (years)	Mean ± SD	26.3 ± 5.12	26.3 ± 5.12
	Range	18-39	18-39
Age Groups	< 18	0	0
	18 – 40	46 (100.0 %)	46 (100.0 %)
	41 – 64	0	0
	65 – 75	0	0
	> 75	0	0
Sex	Male	46 (100.0%)	46 (100.0%)
	Female	0 (0%)	0 (0%)
Race	Asian	0	0
	Black	0	0
	Caucasian	46 (100.0%)	46 (100.0%)
	Hispanic	0	0
	Other	0	0
BMI	Mean ± SD	22.05 ± 1.979	22.05 ± 1.979
	Range	18.6 – 24.8	18.6 – 24.8
Other Factors		NA	NA

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Study No. H216-12					
Subject Number	Reason for Dropout/Replacement	Period	Time (hrs) & Date of dropout	Treatment Missed	Replaced?
(b) (6)	Subject withdrawn from the study due to AE (upper abdominal discomfort & vomiting).	01 In-house	13:35 (b) (6)	R	No
	Subject had an episode of vomiting. Hence withdrawn from the study	01 In-house	10:09 (b) (6)	T	No

(b) (6)	Subject did not report to the facility for period 02; hence considered as drop-outs.	02 Check-in	NA (b) (6)	T	No
	Subject withdrawn from the study due to AE (upper abdominal discomfort & vomiting).	01 Wash-out	08:35 (b) (6)	T	No
	Subject did not report to the facility for period 02; hence considered as drop-outs.	02 Check-in	NA (b) (6)	R	No
	Subject withdrawn from the study due to AE (loose stools).	01 Wash-out	18:45 (b) (6)	T	No

Reviewer's Notes: Subjects No. (b) (6) withdrew consent on their accord in person prior to period I dosing. These two subjects were replaced with Subjects (b) (6), who were later allotted as Subjects No (b) (6) respectively. This was acceptable.

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	**Reported Incidence by Treatment Groups**		
	Fasting Bioequivalence Study No. H216-12		
	Test (T) N=48	**Reference (R) N=50**	**NA# N=52**
Nervous system disorders			
Dizziness	05 (10.4%)	06 (12.0%)	-
Gastrointestinal disorders			
Upper Abdominal discomfort	01 (2.1%)	01 (2.0%)	-
Vomiting	01 (2.1%)	02 (4.0%)	-
Nausea	-	03 (6.0%)	-
Loose stools	-	01 (2.0%)	-
Injury, poisoning and procedural complications			
Injury left elbow		-	01 (1.9%)
Investigations			
Absolute Eosinophil count increased	-	-	01 (1.9%)
Total	**07 (14.6%)**	**13 (26.0%)**	**02 (3.8%)**

NA# - clinically significant abnormal laboratory parameters evaluated during post study safety assessment, which could not be assigned to any one treatment.

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
(b) (6)	T	01	All three subjects were dropped from the study due to AEs; therefore do not affect the study outcome.		
	R	01			
	R	01 (Wash-out)			

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☒ No ☐ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.1.2.4 Protocol Deviations

Study No.: H216-12		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Sampling Time Point Protocol Deviations Period 01	(b) (6)	
Sampling Time Point Protocol Deviations Period 02		

Other Deviations:

Deviation in recording Audio-Video surveillance system:

As per protocol section 12.2, "The whole Informed Consent Process was to be done under Audio Video Surveillance". However, Informed Consent Obtaining was carried under Audio-Video surveillance system, but audio was not recorded.

Reason for deviation: On the day of period 01 check-in dated on 15 Dec 2013 after reporting the volunteers being enrolled in to the study, obtaining informed consent process was carried out by under Audio-Video surveillance system. Later on while checking the data it was found that the audio of one of the interaction with volunteers was not recorded due to technical error.

Impact analysis: There was no impact on the study out come and technical error in audio-video surveillance system was identified and rectified the same.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK	☒ Actual ☐ Nominal

parameters is border line, please reanalyze data using actual sampling time	

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Repeat analysis
		Bioanalytical Method Validation
		Preparation, Distribution and Storage of CC Standards and QC Page 1 of 12 Samples
		Project Sample Analysis, Data Checkup and Acceptance Criteria
		Incurred sample reanalysis and reporting

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Fasting Bioequivalence Study No. H216-12 Analyte Name- Iloperidone								
Parameter	**Standard Curve Samples**							
Standard IDs	STD 8	STD 7	STD 6	STD 5	STD 4	STD 3	STD 2	STD 1
Concentration (pg/mL)	19.846	56.541	282.706	1177.943	2141.715	3294.947	4393.262	5020.871
Inter day Precision (% CV)	2.0	5.5	3.6	2.8	1.7	1.7	2.5	2.7
Inter day Accuracy (% Bias)	0.0	0.6	-3.3	1.4	2.0	1.1	-2.3	0.5
Linearity (r^2)	0.994988 – 0.999618							
Linearity Range (pg/mL)	19.846 – 5020.871							
Sensitivity/LOQ (pg/mL)	19.846							

Analyte Name- Iloperidone				
Parameter	**Quality Control Samples**			
Quality Control Sample IDs	LQC	MQC	M2QC	HQC
Concentration (pg/mL)	57.442	499.493	1997.970	4251.001
Inter day Precision (% CV)	7.5	7.3	7.2	7.0

Inter day Accuracy (% Actual)	100.1	102.3	103.4	102.8

Fasting Bioequivalence Study No. H216-12 Analyte Name - Iloperidone metabolite P88								
Parameter	**Standard Curve Samples**							
Standard IDs	STD 8	STD 7	STD 6	STD 5	STD 4	STD 3	STD 2	STD 1
Concentration (pg/mL)	19.810	56.439	282.194	1175.810	2137.836	3288.979	4385.305	5011.777
Inter day Precision (% CV)	1.4	4.0	2.1	2.0	1.3	1.4	1.3	1.5
Inter day Accuracy (% Bias)	-0.2	0.7	-1.7	1.6	0.6	0.6	-1.9	0.2
Linearity (r^2)	0.998308 – 0.999878							
Linearity Range (pg/mL)	19.810 – 5011.777							
Sensitivity/LOQ (pg/mL)	19.810							

Analyte Name - Iloperidone metabolite P88				
Parameter	**Quality Control Samples**			
Quality Control Sample IDs	LQC	MQC	M2QC	HQC
Concentration (pg/mL)	57.284	498.125	1992.500	4239.362
Inter day Precision (% CV)	6.5	6.6	6.8	6.8
Inter day Accuracy (% Actual)	99.2	98.7	99.0	97.2

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No Multiple peaks without interfering were observed in the chromatograms for analytes and ISTD.
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Fasting Bioequivalence Study No. H216-12 Iloperidone Analytical Report Page No 135 of 136		
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	00	00	0.000	0.000	00	00	0.000	0.000
ISTD variation	27	17	1.270	0.800	27	17	1.270	0.800
Total	**27**	**17**	**1.270**	**0.800**	**27**	**17**	**1.270**	**0.800**

Total No. of samples analyzed: 2126

Fasting Bioequivalence Study No. H216-12 Iloperidone metabolite P88 Analytical Report Page No 135 of 136								
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	0.000	0.000	0	0	0.000	0.000
Value above upper limit of CC	2	0	0.094	0.000	2	0	0.094	0.000
ISTD variation	6	3	0.282	0.141	6	3	0.282	0.141
Total	8	3	0.376	0.141	8	3	0.376	0.141

Total No. of samples analyzed: 2126

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters - Reviewer-calculated

Fasting Bioequivalence Study No. H216-12 (Iloperidone)									
Parameter (units)	Test (n=46)				Reference (n=46)				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
AUC0-t (hr*pg/ml)	24314.63	62.47	11075.76	88867.77	23812.83	60.18	10930.76	84796.25	1.02
AUC∞ (hr*pg/ml)	26828.04	63.82	12040.91	98816.48	26240.69	62.00	11962.72	94780.94	1.02
Cmax (pg/ml)	1454.005	49.35	402.75	3553.36	1435.642	42.09	401.68	3275.18	1.01
Tmax* (hr)	2.000	.	1.00	8.00	2.000	.	1.00	5.00	1.00
Kel (hr^{-1})	0.022	34.18	0.00	0.04	0.022	28.86	0.01	0.03	1.00
$T_{1/2}$ (hr)	39.162	69.62	17.81	161.54	36.202	47.49	21.23	119.83	1.08

* Tmax values are presented as median, range

Fasting Bioequivalence Study No. H216-12 (P88)									
Parameter (units)	Test (n=46)				Reference (n=46)				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
AUC0-t (hr*pg/ml)	51272.28	35.45	10465.30	103581.5	50971.27	36.70	9719.07	104632.9	1.01
AUC∞ (hr*pg/ml)	58157.62	34.47	13888.93	115099.0	58500.69	36.37	12189.38	119522.9	0.99
Cmax (pg/ml)	2040.613	48.00	379.92	5427.61	1971.347	47.07	405.89	4785.62	1.04
Tmax* (hr)	3.500	.	1.00	24.00	2.500	.	1.50	8.00	1.40
Kel (hr^{-1})	0.017	27.89	0.01	0.03	0.016	32.80	0.01	0.04	1.08
$T_{1/2}$ (hr)	43.512	26.67	23.42	76.83	47.372	29.03	17.42	90.18	0.92

* Tmax values are presented as median, range

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Geometic Leaset Square Mean Ratios and 90% Confidence Interval of Iloperidone (N=46)

Parameter	Ln-transformed Geometric Least Square Mean		Ratio (T/R)%	90% Confidence Interval	
	Test (T)	Reference (R)		Lower	Upper
C_{max} (pg/mL)	1298.856	1307.874	99.31	89.73	109.92
AUC_{0-t} (pg.hr/mL)	21521.237	21198.302	101.52	98.09	105.08
AUC_{0-INF} (pg.hr/mL)	23742.490	23252.465	102.11	98.13	106.24

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Iloperidone Tablets (No of subjects completed = 46) Dose (2 × 1 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study No. H216-12 (Iloperidone)						
Parameter (units)	**N**	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	46	21521.24	21198.30	1.02	98.09	105.08
AUC∞ (hr *pg/ml)	46	23742.49	23252.46	1.02	98.13	106.24
Cmax (pg/ml)	46	1298.86	1307.87	0.99	89.73	109.92

Iloperidone Tablets (No of subjects completed = 46) Dose (2 × 1 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study No. H216-12 (P88)						
Parameter (units)	**N**	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	46	47740.49	47181.02	1.01	98.06	104.41
AUC∞ (hr *pg/ml)	46	54400.06	54358.11	1.00	97.10	103.15
Cmax (pg/ml)	46	1834.23	1767.49	1.04	97.92	109.98

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	**Iloperidone** **Parameter** / **RMSE** LAUCT 0.0981 LAUCI 0.1133 LCMAX 0.2894 **P88** **Parameter** / **RMSE** LAUCT 0.0895 LAUCI 0.0862 LCMAX 0.1655
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)**	☐ Yes ☒ No
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed)**	☒ Yes ☐ No

Are there first measurable drug concentration as Cmax? **If yes, please comment**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞[12] (Iloperidone)				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	46	0.91	0.68	0.97
Reference	46	0.91	0.77	0.97
Ratio of AUC0-t/AUC∞ (p88)				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	46	0.88	0.75	0.94
Reference	46	0.87	0.72	0.93
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below	3 out of 46 subjects ([(b) (6)]) from test-treatment group and 1 out of 46 subjects ([(b) (6)] from reference-treatment group showed ratio of AUCt/AUC∞ for iloperidone less than 0.80. 4 out of 46 subjects [(b) (6)] from test-treatment group and 1 out of 46 ([(b) (6)] subjects from reference-treatment group showed ratio of AUCt/AUC∞ for metabolite p88 less than 0.80.			

Comments on PK results:

1. Subject [(b) (6)] had measurable concentration for iloperidone at pre-dose (0 hr) in Period II (reference). The 0 h concentration of [(b) (4)] was [(b) (4)] than [(b) (4)]% of Cmax [(b) (4)] for this subject in this period. Therefore the subject was not excluded.

2. There is a median Tmax difference for the metabolite P88 between the test and reference product in the fasting study. The observed median Tmax of the test P88 is 3.50 (range 1.00-24.00) hours versus 2.50 (range 1.50-8.00) hours for the reference product (T/R=1.40). The reviewer checked the individual PK data, the observed Tmax for metabolite P88 ranges from 1.00-8.00 hours except for one subject, subject [(b) (6)] showed Tmax as 24 hours. Similar Tmax was also observed in other in-house ANDAs for P88 (please see the table below). Per RLD labeling this drug product is indicated for [(b) (4)] schizophrenia, the reviewer considered the observed Tmax difference for P88 should not have a clinical impact on efficacy or safety. Therefore the Tmax difference of metabolite P88 under fasting conditions is acceptable.

[12] See individual test to reference ratios of PK Parameters in SAS Output

ANDA #	Fasting study		Fed study	
	T	R	T	R
206890	2.75 (1.50-6.00)	2.00 (1.00-4.00)	5.00 (2.00-10.00)	5.00 (2.00-8.00)
207098	3.75 (2.00-6.00)	3.50 (2.00-4.50)	5.50 (2.67-8.00)	5.50 (3.33-8.00)
207409	4.00 (2.00-8.00)	4.50 (1.00-8.00)	5.00 (4.00-12.00)	8.00 (4.00-12.00)
Current	3.50 (1.00-24.00)	2.50 (1.50-8.00)	5.25 (1.50- 10.00)	4.50 (1.00- 8.03)

3. A total of 4 subjects had AUCt/AUC∞ ratios below 0.8 for the parent drug, iloperidone. The mean AUCt/AUC∞ ratio for iloperidone is more than 0.9 for both test and reference products indicating that the sampling was carried out for a sufficient period of time.

4. The reviewer agrees with the firm's pharmacokinetic and statistical analysis. The 90% confidence intervals for the AUC_{0-t}, AUC∞, and C_{max} geometric mean test/reference ratios for test iloperidone are within acceptable BE limits of 80-125%.

5. The PK parameters of the test and reference products for the active metabolite P88 were comparable in the fasting BE study. Therefore, the metabolite data are supportive.

The fasting BE study is **adequate.**

4.1.1.5 Overall Comment

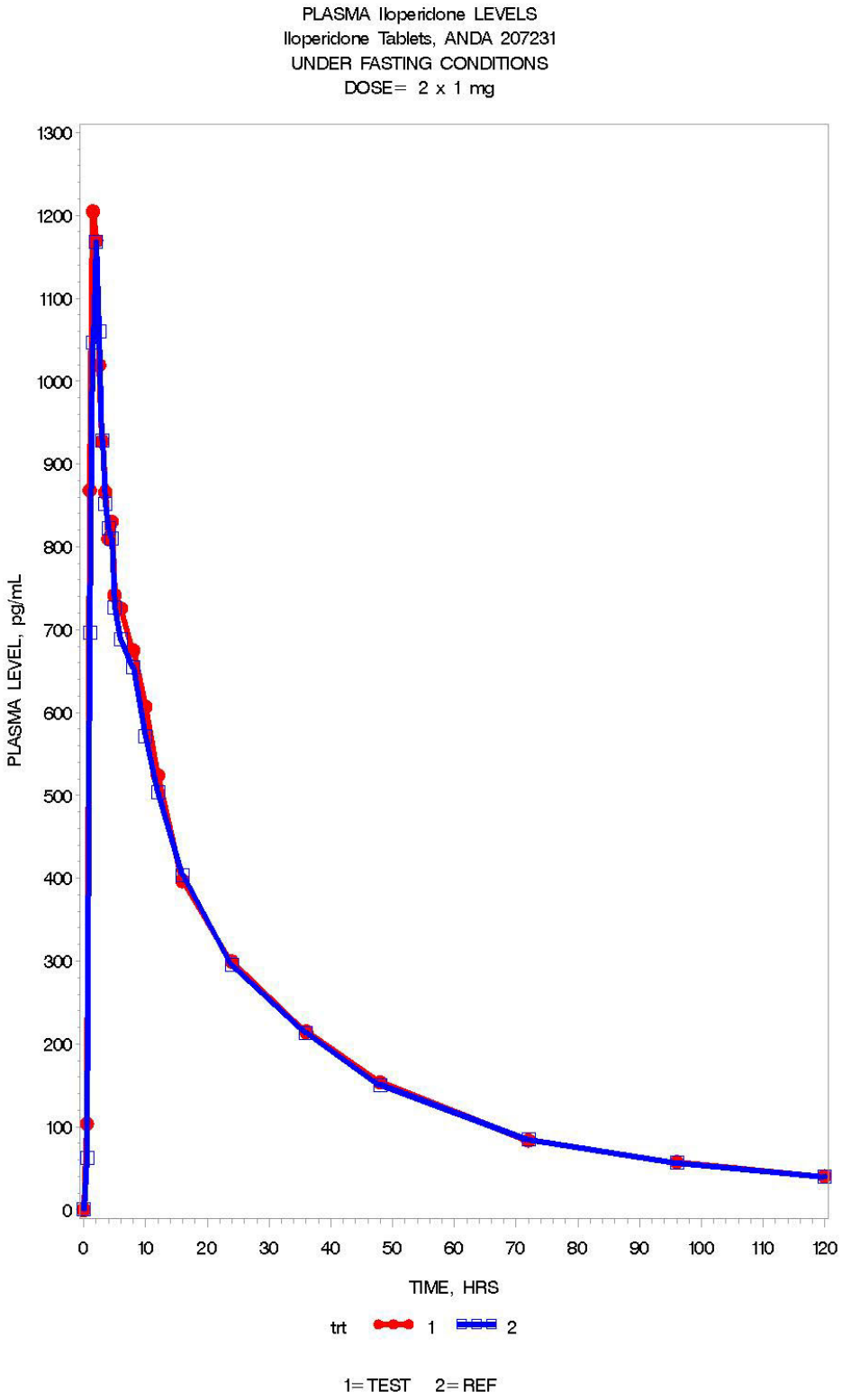
Was the fasting bioequivalence study acceptable? Acceptable

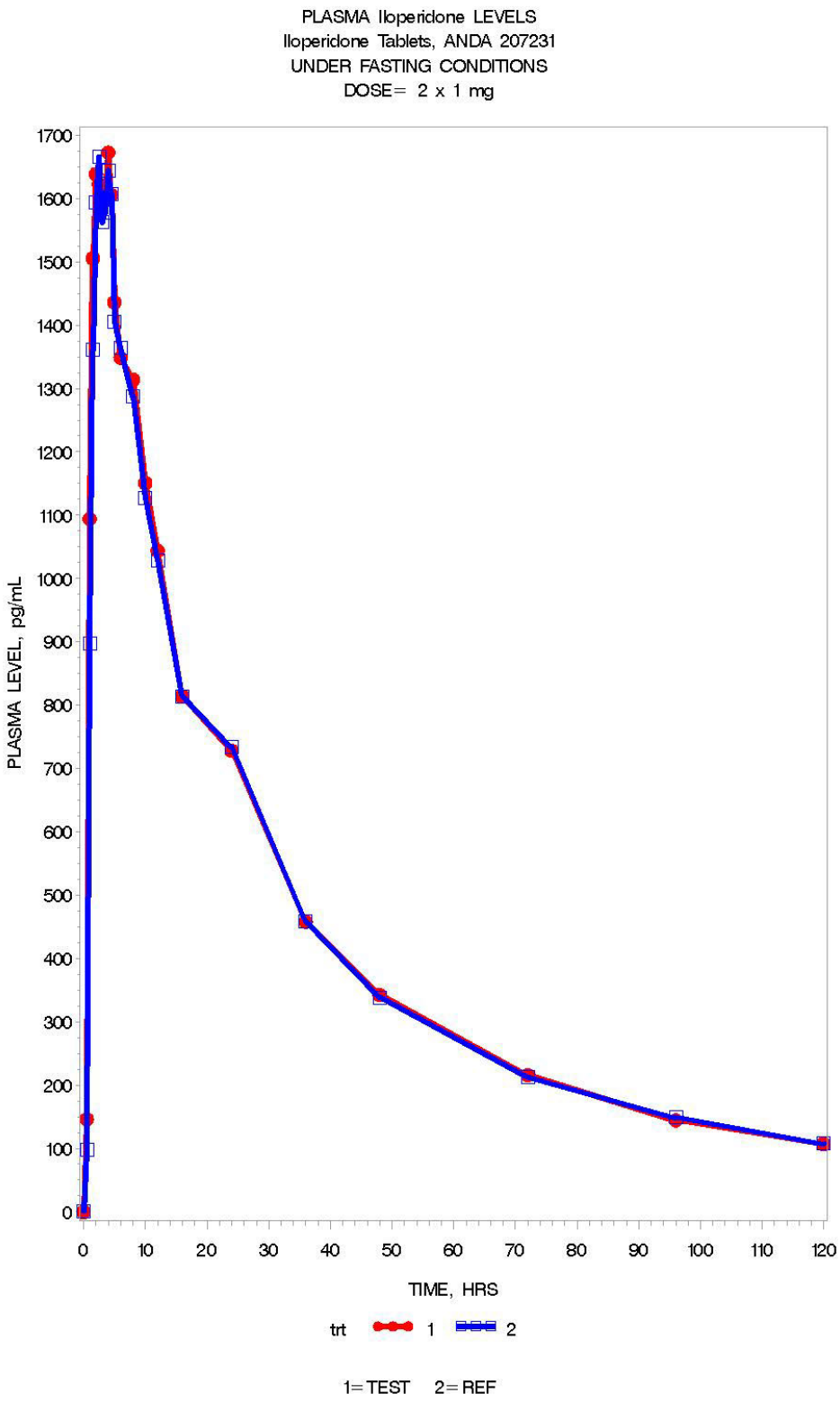
Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Iloperidone Tablets (Iloperidone) Dose (2 × 1 mg)					
Time (hr)	Test (n=46)		Reference (n=46)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	0.00	.	0.51	678.23	0.00
0.50	103.82	87.31	62.83	90.86	1.65
1.00	868.40	76.15	696.10	73.87	1.25
1.50	1205.06	60.00	1046.45	53.01	1.15
2.00	1169.60	47.71	1167.82	42.88	1.00
2.50	1019.58	54.39	1060.43	57.42	0.96
3.00	927.39	55.65	928.32	52.18	1.00
3.50	865.73	60.32	852.23	52.04	1.02
4.00	809.82	56.90	822.96	55.87	0.98
4.50	830.43	57.28	810.01	53.05	1.03
5.00	741.74	52.20	726.26	51.98	1.02
6.00	725.93	58.27	688.58	52.31	1.05
8.00	675.08	59.10	654.70	57.46	1.03
10.00	607.12	60.79	571.31	55.53	1.06
12.00	524.33	67.94	503.70	60.48	1.04
16.00	396.86	63.28	404.04	66.11	0.98
24.00	299.59	68.61	295.01	68.30	1.02
36.00	215.07	64.40	213.79	64.62	1.01
48.00	153.88	66.97	150.59	68.68	1.02
72.00	83.82	80.59	84.56	78.05	0.99
96.00	57.70	79.80	56.51	83.92	1.02
120.00	40.53	88.88	40.35	87.23	1.00

Iloperidone Tablets (Metabolite P88) Dose (2 × 1 mg)					
Time (hr)	Test (n=46)		Reference (n=46)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	0.00	.	0.94	474.35	0.00
0.50	146.52	136.16	97.97	157.78	1.50
1.00	1094.07	105.44	897.56	110.04	1.22
1.50	1506.01	70.75	1361.54	75.67	1.11
2.00	1638.66	54.57	1593.44	56.25	1.03
2.50	1622.31	40.81	1665.97	45.57	0.97
3.00	1613.95	37.24	1562.67	42.71	1.03
3.50	1605.46	35.69	1578.16	39.61	1.02
4.00	1672.67	33.31	1644.12	37.73	1.02
4.50	1605.79	33.21	1607.62	36.77	1.00
5.00	1436.45	33.20	1405.57	35.26	1.02
6.00	1349.04	34.58	1364.15	38.89	0.99
8.00	1314.07	38.30	1287.57	36.30	1.02
10.00	1150.91	35.58	1127.04	36.75	1.02
12.00	1043.90	35.60	1028.88	34.77	1.01
16.00	813.79	36.41	814.00	37.74	1.00
24.00	728.48	37.03	733.76	37.10	0.99
36.00	458.39	38.85	458.23	41.11	1.00
48.00	342.75	38.31	338.36	40.99	1.01
72.00	216.11	38.68	212.60	43.81	1.02
96.00	144.57	38.65	149.23	43.34	0.97
120.00	107.29	40.35	107.87	40.39	0.99

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study




PLASMA Iloperidone LEVELS
Iloperidone Tablets, ANDA 207231
UNDER FASTING CONDITIONS
DOSE= 2 x 1 mg
PLASMA LEVEL, pg/mL
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0 10 20 30 40 50 60 70 80 90 100 110 120
TIME, HRS
trt 1 2
1=TEST 2=REF

4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	H217-12
Study Title	Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover pivotal oral bioequivalence study of Iloperidone Tablets (2x1 mg) of Inventia Healthcare Pvt Ltd., India and Fanapt® iloperidone tablets (2x1 mg) (b) (4) Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 in normal, healthy, adult, human subjects under fed condition.
Clinical Site (Name & Address)	Clinical Pharmacology Unit GVK BIOSCIENCES PVT. LTD. 1st& 7th Floor, Swarna Jayanthi Commercial Complex Ameerpet, Hyderabad – 500 038, India. Phone No.: +91-40-6627-5555 Fax No.: +91-40-6627-5599
Principal Clinical Investigator	Dr. Ch. Nagaratnam, MD nagaratnam.chitibomma @gvkbio.com Dr. T. Ajit Singh, MD General Medicine (UKr), PGDHSc in Diabetology ajitsingh.thakur@gvkbio.com
Dosing Dates	Period 01 : 24 Oct 2013 Period 02: 08 Nov 2013
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	
Principal Analytical Investigator	
Sample Storage : **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	72 days (Iloperidone) 75 days (Iloperidone Metabolite P88) –70 ± 20°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Iloperidone: 79 days @ –2 to 8° Iloperidone Metabolite P88: 79 days @ –2 to 8°C

4.1.2.1.2 Product Information

NA (Include only if product information is different from the fasting study.)

4.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 74 (with two additional subjects (b) (6) Dosed: 72 in Period I[13], 66 in Period II[14] Completed: 66 Samples Analyzed: 72 Statistically Analyzed: 72 for PK analysis, 66 for BE evaluation	
No. of Sequences	2 (sequence 1 TR; sequence 2 RT)	
No. of Periods	2	
No. of Treatments	2	
No. of Groups	1	
Washout Period	15 days	
Randomization	☒ Yes ☐ No	
Blood Sampling Times	Twenty five blood samples were collected from each subject during each period at pre-dose (0.00) and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00, 96.00 and 120.00 hours after dosing.	
IRB Approval	☒ Yes Date: Protocol- approved 24 Sep 2013	☐ No
Informed Consent	☒ Yes Date: Written informed consent was obtained from each subject before screening and before enrolling in the study (before check-in for the first period i.e. on 23 Oct 2013). ☐ No	
Length of Fasting	Fasted for at least 10 hours prior to a high fat breakfast. Dosing was done 30 minutes after the start of the breakfast.	
Length of Confinement	In both the study periods, subjects were housed at the clinical facility from not less than 11 hours pre-dose till 48 hours post-dose.	
Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A	
Safety Monitoring	☒ Yes ☐ No	

Standard FDA Meal Used?	☐ Yes ☒ No
If No, then meal components and composition is listed in the tables below	

[13] Subject No. (b) (6) was withdrawn from the study prior to period I dosing due to AE, he was replaced with Subject (b) (6), who was later allotted Subject No. (b) (6)
[14] Subjects No. (b) (6) were withdrawn from the study in Period I due to AEs. Subjects No. (b) (6) did not report to the facility for period II checked in.

Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study

Composition of Meal Used in Non Fasted Bioequivalence Study (Study No. H217-12)		
Composition	**Percent of total Kcal**	**Kcal**
Protein	15.05	143.32
Fat	55.60	529.56
Carbohydrates	29.35	279.52
Total Energy (Kcal)	**100.00**	**952.40**

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study H217-12

Meal ID: H217/02	Meal Type: Fed breakfast
S.No	Food Item	Portion Size (Cooked weight)
1	Bread slice with butter	2 no.
2	Fried chicken	¼ cup
3	Egg	2 no.
4	French Fries	1 cup
5	Milk	1 glass

Nutritive value of food items (Raw weight)

S.No	Food item	Quantity (gm)/(ml)	Protein (Gram)	Fat (Gram)	Carbohydrates (Gram)
1	Wheat bread (white)	40	3.12	0.28	20.76
2	Chicken	50	12.95	0.30	0.00
3	Egg	80	10.64	10.64	0.00
4	Potato	120	1.92	0.12	27.12
5	Milk (Whole milk)	240	7.20	14.40	12.00
6	Sugar	10	0.00	0.00	10.00
7	Oil	25	0.00	25.00	0.00
8	Butter	10	0.00	8.10	0.00
Total			35.83	58.84	69.88
Energy (Kcal)			143.32	529.56	279.52
Total Energy (Kcal)			952.40		
Percentage of Caloric Content			15.05	55.60	29.35

Reviewer's Note: This information was taken from page 146 of the study report and page 55 of the study protocol.

Comments on Study Design: Adequate

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Fed Bioequivalence Study No. H217-12		
	Treatment Groups	
	Test Product	**Reference Product**

		N = 66	N = 66
Age (years)	**Mean ± SD**	26.0 ± 5.48	26.0 ± 5.48
	Range	18-41	18-41
Age Groups	**< 18**	< 18	< 18
	18 – 40	18-40	18-40
	41 – 64	41-64	41-64
	65 – 75	65-75	65-75
	> 75	>75	>75
Sex	**Male**	66 (100 %)	66 (100 %)
	Female	0 (0%)	0 (0%)
Race	**Asian**	0	0
	Black	0	0
	Caucasian	66 (100%)	66 (100 %)
	Hispanic	0	0
	Other	0	0
BMI	**Mean ± SD**	22.42 ± 2.095	22.42 ± 2.095
	Range	18.6-24.9	18.6-24.9
Other Factors		NA	NA

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation?	☒ Yes ☐ No

4.1.2.2.2 Dropout Information

Study No. H217-12						
Subject Number	**Reason for Dropout/Replacement**	**Period**	**Time (hrs) & Date of dropout**	**Treatment Missed**	**Replaced ?**	**Replaced with**
(b) (6)	Subject withdrawn from the study due to AE (Dizziness- Acute on set Vasovagal) before dosing at and he was replaced with subject number (b) (6)	01 In-house Before dosing	08:05 (b) (6)	TR	Yes	Subject # (b) (6)
	Subject withdrawn from the study due to AE (Vomiting) during period 01 in-house.	01 In-house	10:30 (b) (6)	R	No	NA
	Subject withdrawn from the study due to AE (Dizziness and injury below the chin) during period 01 in-house.	01 In-house	16:22 (b) (6)	R	No	NA
	Subject withdrawn from the study due to AE (Rash) during period 01 in- house.	01 In-house	11:00 hrs on (b) (6)	R	No	NA

(b) (6)	Subject withdrawn from the study due to AE (Fever) during period 01 wash-out.	01 Wash-out	18:12 (b) (6)	T	No	NA
	Subject withdrawn from the study due to AE (Rash) during period 01 wash-out.	01 Wash-out	18:34 (b) (6)	R	No	NA
	Subject failed to report to the clinical facility for period 02 Check- in.	02 Check- in	NA (b) (6)	R	No	NA

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.2.2.3 Study Adverse Events

Body System / Adverse Event	**Reported Incidence by Treatment Groups**			
	Fed Bioequivalence Study No. H217-12			
	Test N=71	**Reference N=67**	**NA***	**NA# N=72**
Nervous system disorders				
Dizziness	06 (8.4%)	05 (7.5 %)	--	--
Headache	01 (1.4 %)	02 (3.0%)	--	--
Somnolence	02 (2.8%)	07 (11.9%)	--	--
Gastrointestinal system disorders				
Vomiting	01 (1.4 %)	--	--	--
Nausea	--	01 (1.5 %)	--	--
Vascular disorders				
Acute onset vasovagal	--	--	01 (1.4 %)	--
Skin and subcutaneous tissue disorders				
Rash	02 (2.8 %)	--	--	--
Injury below the chin	01 (1.4 %)	--	--	--
General disorders and administration site conditions				
Fever	--	01 (1.5 %)	--	--
Investigations				
Nil	--	--	--	--
Total	**13 (11.2%)**	**16 (25.5%)**	**01 (1.4%)**	--

NA*- Pre-dose adverse event (period 01)
NA# - clinically significant abnormal laboratory parameters evaluated during post study safety assessment, which could not be assigned to any one treatment.

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	**Test/ Reference**	**Period**	**Time and Date of dosing**	**Time and Date of emesis**	**Duration Between Dosing and Start of**

					Emesis (hours)
(b) (6)	T	01	This subject was dropped from the study due to vomiting; therefore do not have impact on the study outcome		

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☒ No ☐ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.2.2.4 Protocol Deviations

Study No.: H217-12		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Sampling Time Point Protocol Deviations Period 01	(b) (6)	
Sampling Time Point Protocol Deviations Period 02		

Other Deviations:

Deviation: As per protocol section 8.2 states that "A reduction in systolic blood pressure of at least 20 mm Hg or in diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing was considered as orthostatic hypotension". However, in period 01, for subject number (b) (6) reduction in diastolic Blood pressure is more than 10 mm of Hg at the time of period 01 check-in orthostatic vitals.

Reason: Inadequately missed the vitals due to oversight.

Impact analysis: Both the subjects were not having any complaints like dizziness during vital signs measurement (standing and supine BP). Standing BP was within acceptable range as specified in protocol (section 5.1 & 5.2) for both the subjects. And also screening and pre-dose vitals in both the periods is also within normal limits. Hence there is no impact on the safety of study subjects. And subject number (b) (6) was not having any AE's during the study and subject number (b) (6) having nausea and resolved un eventually. And both the subjects checked out in both the periods in Heamodynamically stable condition.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Provide only if the SOPs are different from the fasting study.

4.1.2.3.2 Sample Analysis Calibration and Quality Control

Fasting Bioequivalence Study No. H217-12 Analyte Name - Iloperidone								
Parameter	**Standard Curve Samples**							
Standard IDs	STD 8	STD 7	STD 6	STD 5	STD 4	STD 3	STD 2	STD 1
Concentration (pg/mL)	20.017	56.498	282.489	1177.039	2140.071	3292.417	4389.890	5017.017
Inter day Precision (% CV)	1.4	4.1	3.6	2.3	1.9	2.0	2.0	2.6
Inter day Accuracy (% Bias)	1.1	-3.1	-0.4	0.8	1.1	1.0	1.0	-1.6
Linearity (r^2)	0.996055 – 0.999892							
Linearity Range (pg/mL)	20.017-5017.017							
Sensitivity/LOQ (pg/mL)	20.017							

Analyte Name - Iloperidone				
Parameter	**Quality Control Samples**			
Quality Control Sample IDs	LQC	MQC	M2QC	HQC
Concentration (pg/mL)	57.917	500.144	2000.577	4247.509
Inter day Precision (% CV)	8.5	7.8	5.6	6.4
Inter day Accuracy (% Actual)	95.2	100.0	101.9	102.2

Fasting Bioequivalence Study No. H217-12 Analyte Name - Iloperidone metabolite P88								
Parameter	**Standard Curve Samples**							
Standard IDs	STD 8	STD 7	STD 6	STD 5	STD 4	STD 3	STD 2	STD 1
Concentration (pg/mL)	20.008	56.471	282.356	1176.485	2139.064	3290.867	4387.823	5014.655
Inter day Precision (% CV)	1.4	3.8	2.5	2.1	1.6	1.4	1.7	2.6
Inter day Accuracy (% Bias)	0.2	-0.2	-1.0	0.6	0.5	0.4	0.2	-0.4
Linearity (r^2)	0.996428 – 0.999872							
Linearity Range (pg/mL)	20.008 – 5014.655							

Sensitivity/LOQ (pg/mL)	20.008

Analyte Name - Iloperidone metabolite P88				
Parameter	**Quality Control Samples**			
Quality Control Sample IDs	LQC	MQC	M2QC	HQC
Concentration (pg/mL)	57.463	496.230	1984.921	4214.269
Inter day Precision (% CV)	6.1	6.9	4.9	5.7
Inter day Accuracy (% Actual)	97.7	99.2	101.4	101.3

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.2.3.3 Reanalysis of Study Samples

Fasting Bioequivalence Study No. H217-12 Iloperidone Analytical Report Page No 170 of 171								
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	0.000	0.000	0	0	0.000	0.000
ISTD variation	50	55	1.468	1.615	50	55	1.468	1.615
Instrumental error	2	0	0.059	0.000	2	0	0.059	0.000
Deviated sample	5	4	0.147	0.117	5	4	0.147	0.117
Total	**57**	**59**	**1.674**	**1.732**	**57**	**59**	**1.674**	**1.732**

Total No. of samples analyzed: 3406

Fasting Bioequivalence Study No. H217-12 Iloperidone metabolite P88 Analytical Report Page No 170 of 171				
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	0.000	0.000	0	0	0.000	0.000
ISTD variation	12	6	0.352	0.176	12	6	0.352	0.176
Instrumental error	2	0	0.059	0.000	2	0	0.059	0.000
Deviated sample	2	0	0.059	0.000	2	0	0.059	0.000
Total	16	6	0.470	0.176	16	6	0.470	0.176

Total No. of samples analyzed: 3406

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate

(Please comment if any of above items need additional comments)

4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters - Reviewer Calculated

Fed Bioequivalence Study No. H217-12 (Iloperidone)									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**%CV**	**Min**	**Max**	
AUC0-t (hr*pg/ml)	25704.14	33.33	9201.93	55008.15	26060.61	34.42	7961.61	53812.63	0.99
AUC∞ (hr*pg/ml)	27726.39	33.35	10775.70	59363.96	28258.69	34.20	8579.35	58424.89	0.98
Cmax (pg/ml)	1334.769	39.39	379.19	3001.88	1470.085	46.31	458.01	2914.27	0.91
Tmax* (hr)	4.500	.	1.00	8.00	3.500	.	1.00	6.00	1.29
Kel (hr^{-1})	0.023	27.73	0.01	0.04	0.023	31.10	0.01	0.04	1.02
$T_{1/2}$ (hr)	33.243	43.19	16.59	116.50	34.349	39.34	17.62	70.86	0.97

* Tmax values are presented as median, range

Fed Bioequivalence Study No. H217-12 (P88)									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**%CV**	**Min**	**Max**	
AUC0-t (hr*pg/ml)	66668.96	28.91	32051.65	130569.3	67645.68	26.52	28688.82	113092.9	0.99
AUC∞ (hr*pg/ml)	76375.02	28.90	40273.35	151523.4	77588.36	28.55	34217.06	149212.3	0.98
Cmax (pg/ml)	2142.015	29.00	900.48	4167.03	2205.832	24.86	884.29	3329.75	0.97

Tmax* (hr)	5.250	.	1.50	10.00	4.500	.	1.00	8.03	1.17
Kel (hr^{-1})	0.017	28.30	0.01	0.03	0.016	22.93	0.01	0.03	1.01
$T_{1/2}$ (hr)	45.670	32.86	24.22	104.95	44.961	26.66	25.37	81.12	1.02

* Tmax values are presented as median, range

4.1.2.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Geometic Leaset Square Mean Ratios and 90% Confidence Interval of Iloperidone (N=66)

Parameter	Ln-transformed Geometric Least Square Mean		Ratio (T/R)%	90% Confidence Interval	
	Test (T)	Reference (R)		Lower	Upper
C_{max} (pg/mL)	1235.140	1322.776	93.37	87.69	99.43
AUC_{0-t} (pg.hr/mL)	24319.617	24641.239	98.69	96.55	100.89
AUC_{0-INF}(pg.hr/mL)	26260.637	26748.581	98.18	95.87	100.54

4.1.2.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Iloperidone Tablets (No of subjects completed = 66) Dose (2 × 1 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study No. H217-12 (Iloperidone)						
Parameter (units)	**N**	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	66	24319.62	24641.24	0.99	96.55	100.89
AUC∞ (hr *pg/ml)	66	26260.64	26748.58	0.98	95.87	100.54
Cmax (pg/ml)	66	1235.14	1322.78	0.93	87.69	99.43

Iloperidone Tablets (No of subjects completed = 66) Dose (2 × 1 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study No. H217-12 (P88)						
Parameter (units)	**N**	**Test**	**RLD**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	66	63956.49	65265.35	0.98	96.11	99.92
AUC∞ (hr *pg/ml)	66	73285.47	74597.09	0.98	96.12	100.41
Cmax (pg/ml)	66	2058.48	2133.44	0.96	93.34	99.74

4.1.2.4.4 Additional Information for the Study

Root Mean Square Error	Iloperidone	Parameter	RMSE

	[redacted] LAUCT 0.0754 LAUCI 0.0816 LCMAX 0.2157 P88 / Parameter / RMSE LAUCT 0.0668 LAUCI 0.0752 LCMAX 0.1139
Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)	☐ Yes ☒ No Please see comments below.
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed)	☒ Yes ☐ No
Are there first measurable drug concentration as Cmax? If yes, please comment	☒ Yes ☐ No Subject (b) (6) of reference product for parent compound
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞[15] (Iloperidone)				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	66	0.93	0.75	0.97
Reference	66	0.92	0.74	0.97
Ratio of AUC0-t/AUC∞ (p88)				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	66	0.87	0.74	0.94
Reference	66	0.88	0.74	0.95
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below	1 out of 66 subjects (b) (6) from test-treatment group and 1 out of 66 subjects (b) (6) from reference-treatment group showed ratio of AUCt/AUC∞ for iloperidone less than 0.80. 5 out of 66 subjects [redacted] (b) (6) from test-treatment group and 5 out of 66 (b) (6) subjects from reference-treatment group showed ratio of AUCt/AUC∞ for metabolite p88 less than 0.80.			

Comments on PK results: Adequate

[15] See individual test to reference ratios of PK Parameters in SAS Output

1. Per the RLD labeling, administration of iloperidone with a standard high-fat meal would delay the Tmax by 1 hour for iloperidone and 2 hours for P88. The observed median Tmax for iloperidone and P88 in the fed study are consistent with the RLD labeling.

2. There is a median Tmax difference for the parent drug, iloperidone between the test and reference product in the fed study. The observed median Tmax (range) of the test product is 4.50 (1.00-8.00) hours versus 3.50 (1.00-6.00) hours for the reference product (T/R=1.29). Per the RLD labeling, the Tmax for iloperidone is 2-4 hours, and is indicated for (b) (4) for schizophrenia. The reviewer considered the observed difference in Tmax should not have a clinical impact on efficacy or safety. Therefore the Tmax difference of iloperidone under fed conditions is acceptable.

3. Subject (b) (6) had measurable concentration for iloperidone at pre-dose (0 hr) in Period II (test). The 0 h concentration of (b) (4) % of Cmax (2224.974 pg/mL) for this subject in this period. Therefore the subject was not excluded.

4. A total of 2 subjects had AUCt/AUC∞ ratios below 0.8 for the parent drug, iloperidone. The mean AUCt/AUC∞ ratio for iloperidone is more than 0.9 for both test and reference products indicating that the firm's sampling schedule was carried out for a sufficient period of time.

5. The reviewer agrees with the firm's pharmacokinetic and statistical analysis. The 90% confidence intervals for the AUC_{0-t}, AUC∞, and C_{max} geometric mean test/reference ratios for test iloperidone are within acceptable BE limits of 80-125%.

6. The PK parameters of the test and reference products for the active metabolite P88 were comparable in the fed BE study. Therefore, the metabolite data are supportive.

The fed BE study is **adequate.**

4.1.2.5 Overall Comment

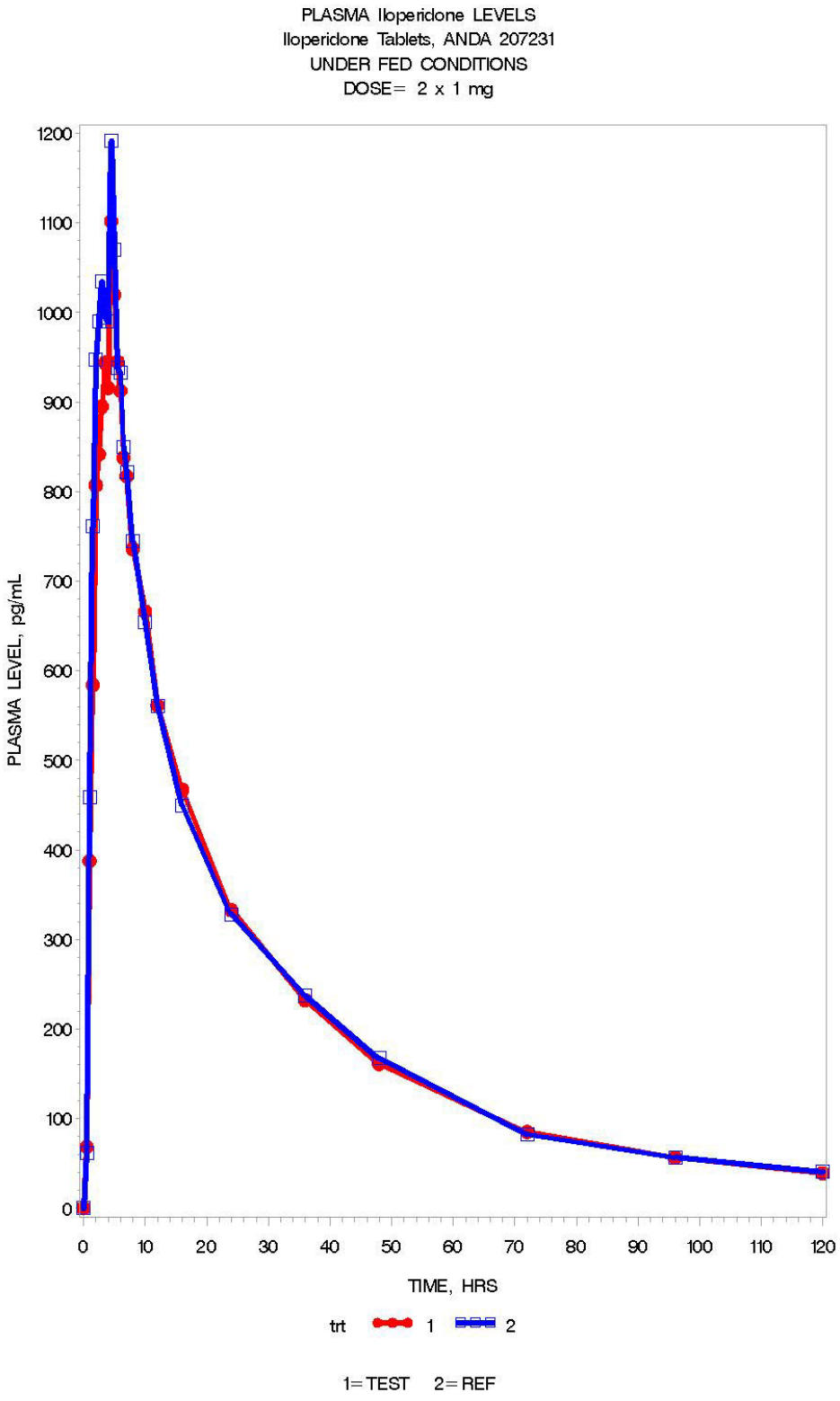
Was the Fed bioequivalence study acceptable? Acceptable

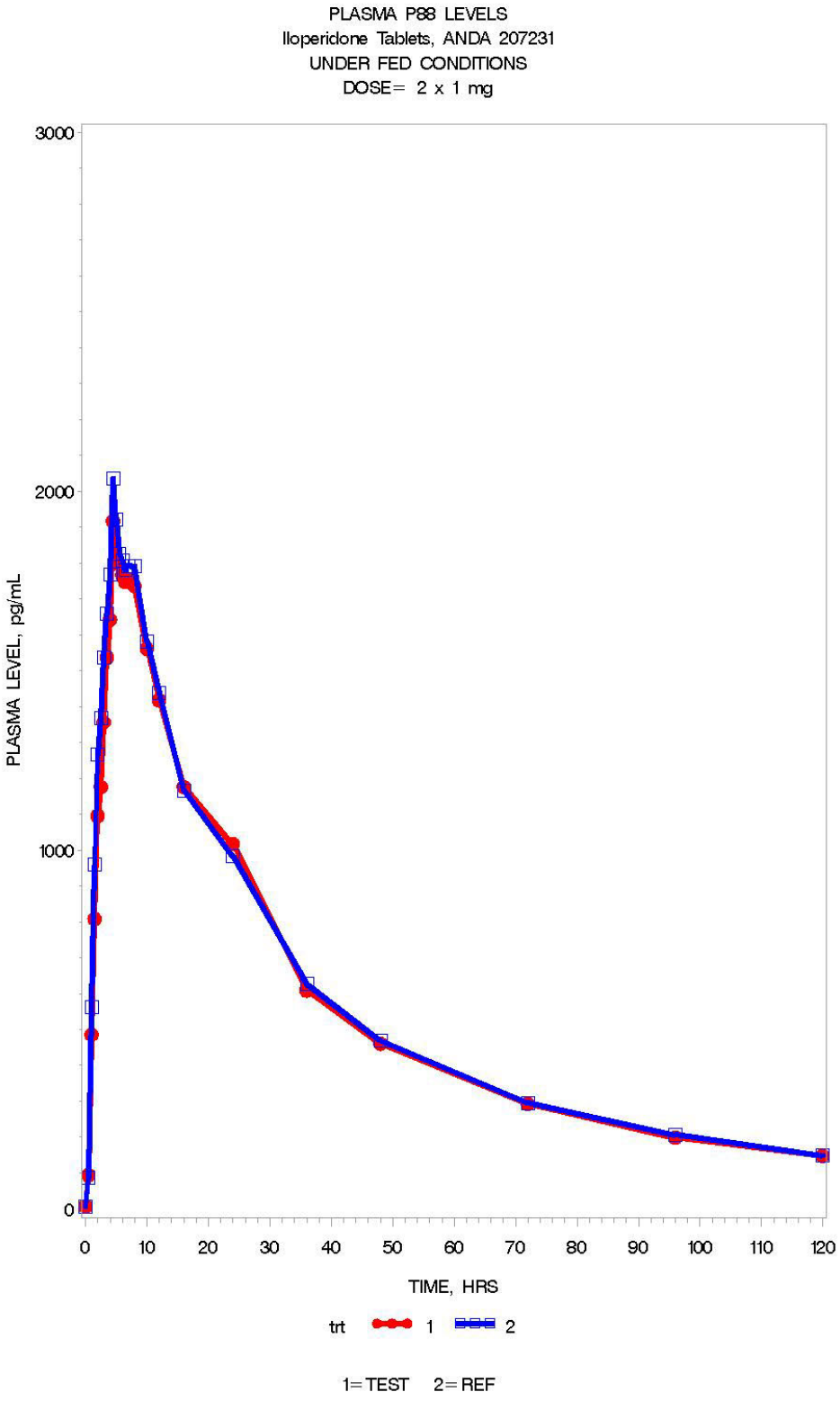
Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Iloperidone Tablets Dose (2 × 1 mg)					
Iloperidone					
Time (hr)	Test (n=66)		Reference (n=66)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	0.45	812.40	0.00	.	.
0.50	68.85	113.51	61.39	129.30	1.12
1.00	388.01	124.76	458.79	102.06	0.85
1.50	584.51	85.39	760.81	87.68	0.77
2.00	807.28	59.47	946.82	63.63	0.85
2.50	841.84	53.12	990.32	58.80	0.85
3.00	895.08	50.11	1034.21	56.23	0.87
3.50	943.79	44.02	993.98	48.37	0.95
4.00	915.82	39.73	989.72	46.73	0.93
4.50	1102.03	44.39	1191.24	44.52	0.93
5.00	1019.83	39.54	1069.87	45.42	0.95
5.50	945.24	37.76	937.81	38.71	1.01
6.00	912.83	37.97	932.28	40.50	0.98
6.50	837.92	35.72	849.52	36.82	0.99
7.00	817.08	35.88	821.10	36.47	1.00
8.00	736.18	34.98	744.62	38.49	0.99
10.00	666.13	34.45	653.90	34.35	1.02
12.00	561.27	37.73	561.14	36.02	1.00
16.00	467.30	36.55	449.91	37.30	1.04
24.00	333.02	30.81	328.15	32.14	1.01
36.00	232.45	38.56	237.22	35.12	0.98
48.00	161.44	38.72	167.35	39.00	0.96
72.00	85.42	46.54	82.48	45.42	1.04
96.00	56.83	46.55	56.88	50.29	1.00
120.00	39.33	49.66	40.73	53.67	0.97

Iloperidone Tablets Dose (2 × 1 mg)					
P88					
Time (hr)	Test (n=66)		Reference (n=66)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	7.37	200.60	6.71	193.99	1.10
0.50	94.64	90.36	86.33	111.99	1.10
1.00	485.50	113.11	562.31	106.14	0.86
1.50	807.98	91.23	958.82	71.96	0.84
2.00	1095.97	64.70	1265.43	55.03	0.87
2.50	1176.58	45.44	1366.77	42.87	0.86
3.00	1356.66	41.67	1537.54	36.98	0.88
3.50	1537.45	33.14	1659.21	34.13	0.93
4.00	1643.10	30.28	1768.49	29.78	0.93
4.50	1916.99	29.41	2035.50	26.66	0.94
5.00	1808.42	28.40	1920.48	26.37	0.94
5.50	1796.97	28.14	1825.52	25.63	0.98
6.00	1766.57	27.61	1806.18	25.96	0.98
6.50	1748.02	26.02	1780.74	24.94	0.98
7.00	1754.64	26.13	1792.64	24.06	0.98
8.00	1736.63	25.26	1791.30	24.04	0.97
10.00	1561.55	25.12	1581.51	27.59	0.99
12.00	1417.96	26.39	1437.15	24.90	0.99
16.00	1176.32	29.18	1166.08	28.59	1.01
24.00	1017.20	30.40	982.41	25.36	1.04
36.00	609.22	36.75	626.81	33.33	0.97
48.00	461.04	36.53	469.19	34.72	0.98
72.00	293.24	42.17	295.33	34.22	0.99
96.00	199.30	39.12	206.53	37.59	0.97
120.00	148.64	38.07	149.22	39.28	1.00

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study (Add profiles for additional API)





1 Page has been withheldin full as b4 (CCI/TS) immediately following this page

(b) (4)

(b) (4)

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☒ Yes ☐ No ☐ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☐ Yes ☒ No
If no, are they all within IIG (per day) limits?	☒ Yes ☐ No ☐ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
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)?	☐ Yes ☐ No ☒ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

Comments on Formulation:

[16] FDA Internal IIG Database, http://intranetapps.test fda.gov/scripts/iig/ last accessed on 02/29/16
[17] NDA 21882 labeling, http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021882s021lbl.pdf, initial U.S. Approval 2005, last accessed 03/01/2016
[18] DARRTS NDA 21882, REV-QUALITY-03(General Review), dated 07/06/2005

The levels of inactive ingredients in the test formulation are lower than that present in the FDA-approved drug products based on CDER's IID.

The 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths of the test formulation are proportionally similar to the 1 mg strength which underwent bioequivalence testing.

There is no elemental iron in the composition of the product, which complies with the element iron limit of not exceeding 5 mg per day according to 21 CFR 73.1200(c).

The firm's formulation is **acceptable**.

4.3 Dissolution Testing (Applicable only if there are waiver requests)

Dissolution data were reviewed separately, and the overall review result is **adequate**. The dissolution review was finalized at GDRP ANDA-207231-ORIG-1, http://panorama.fda.gov/task/view?ID=542129670039f143f84ce04856b9c61f, Biopharmaceutics Primary Review (completion date 14-Mar-2015 and 22-Jun-2015)

Dissolution Data [19]

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)(4)% (Q) dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	Testing Date	Product ID (Test - Manufacture Date, Reference – Expiry Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (mins) 10	15	30	45	60	Study Report Location
Batch No. EXB/618/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg. date: Jul. 2013	1 mg Tablet	12	Mean	96	97	97	97	98	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.4	2.4	3.2	3.4	3.3	
Lot No. FFZN	Nov. 2013	Reference Listed Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	1 mg Tablet	12	Mean	93	94	95	95	95	Section 2.7.1.2
					Range	(b) (4)					
					% CV	3.0	1.9	1.8	1.8	1.6	

[19] Tables are from Dissolution Only Review. The applicant acknowledged the FDA-recommended Dissolution Specification of NLT (b)(4)% (Q) in 30 minutes in its amendment dated June 10, 2015.

Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)(4)% (Q) dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	Testing Date	Product ID (Test - Manufacture Date, Reference – Expiry Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (mins) 10	15	30	45	60	Study Report Location
Batch No. EXB/619/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg. date: Jul. 2013	2 mg Tablet	12	Mean	99	100	101	102	102	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.0	1.4	2.5	2.4	2.6	
Lot No. FFZP	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	2 mg Tablet	12	Mean	94	96	96	97	97	Section 2.7.1.2
					Range	(b) (4)					
					% CV	5.0	3.5	5.0	5.3	4.4	
Batch No. EXB/620/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg. date: Jul. 2013	4 mg Tablet	12	Mean	89	93	97	97	97	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.2	1.9	2.1	2.0	1.7	
Lot No. FFZM	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	4 mg Tablet	12	Mean	92	94	97	97	97	Section 2.7.1.2
					Range	(b) (4)					
					% CV	3.6	2.4	2.3	2.0	2.7	

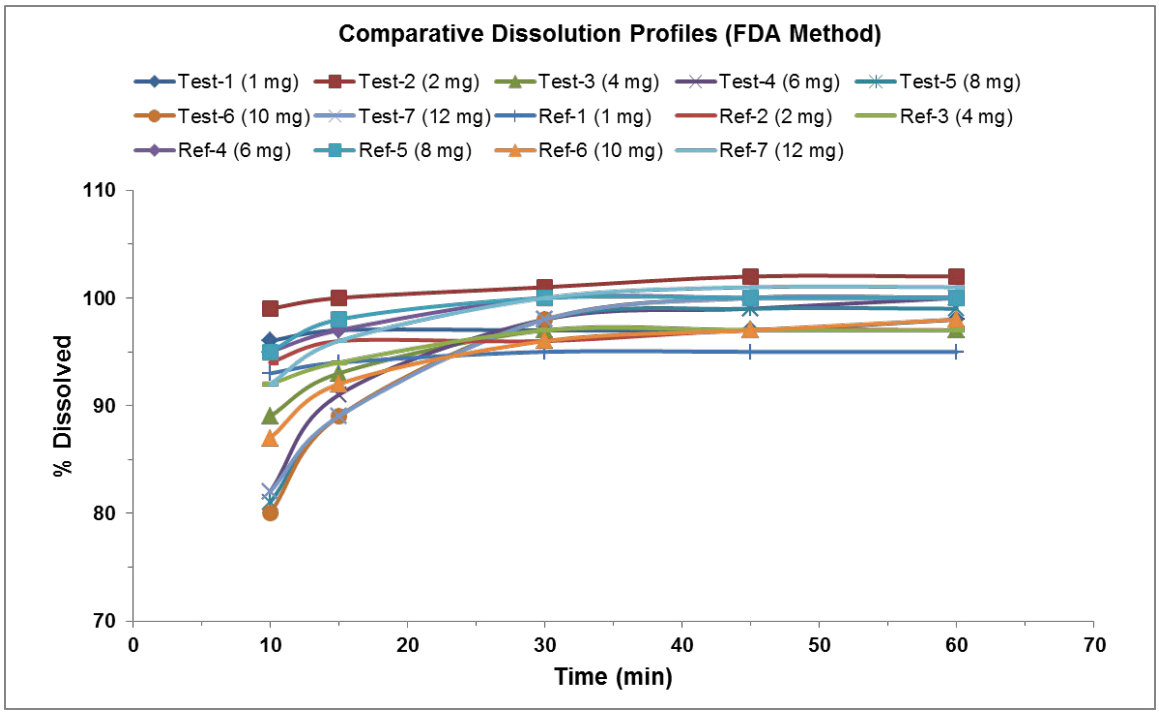
Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)(4)% (Q) dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

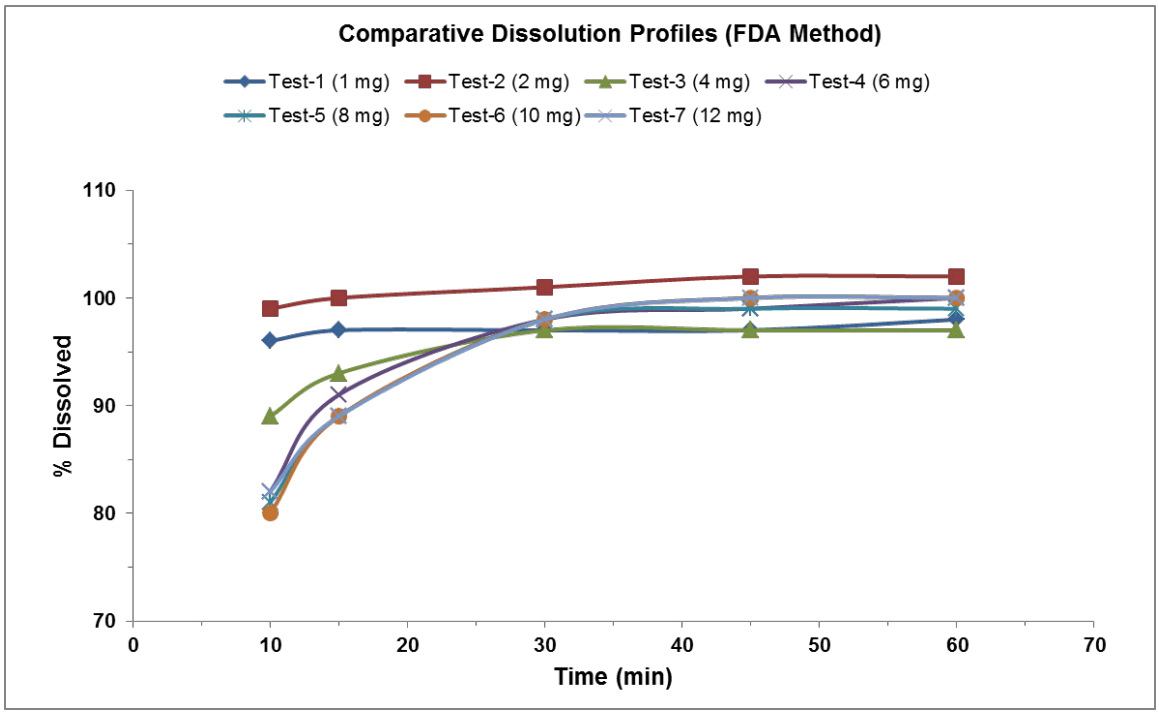
Study Ref No.	Testing Date	Product ID (Test - Manufacture Date, Reference – Expiry Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (mins) 10	15	30	45	60	Study Report Location
Batch No. EXB/621/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg. date: Jul. 2013	6 mg Tablet	12	Mean	82	91	98	99	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	3.5	2.3	2.3	2.2	2.3	
Lot No. FYPB	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Jul. 2014	6 mg Tablet	12	Mean	95	97	100	100	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	1.6	1.3	1.2	1.1	1.2	
Batch No. EXB/622/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg. date: Jul. 2013	8 mg Tablet	12	Mean	81	89	98	99	99	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.6	2.0	1.9	1.2	1.5	
Lot No. FYPC	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	8 mg Tablet	12	Mean	95	98	100	100	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	1.0	1.2	0.7	1.2	1.2	

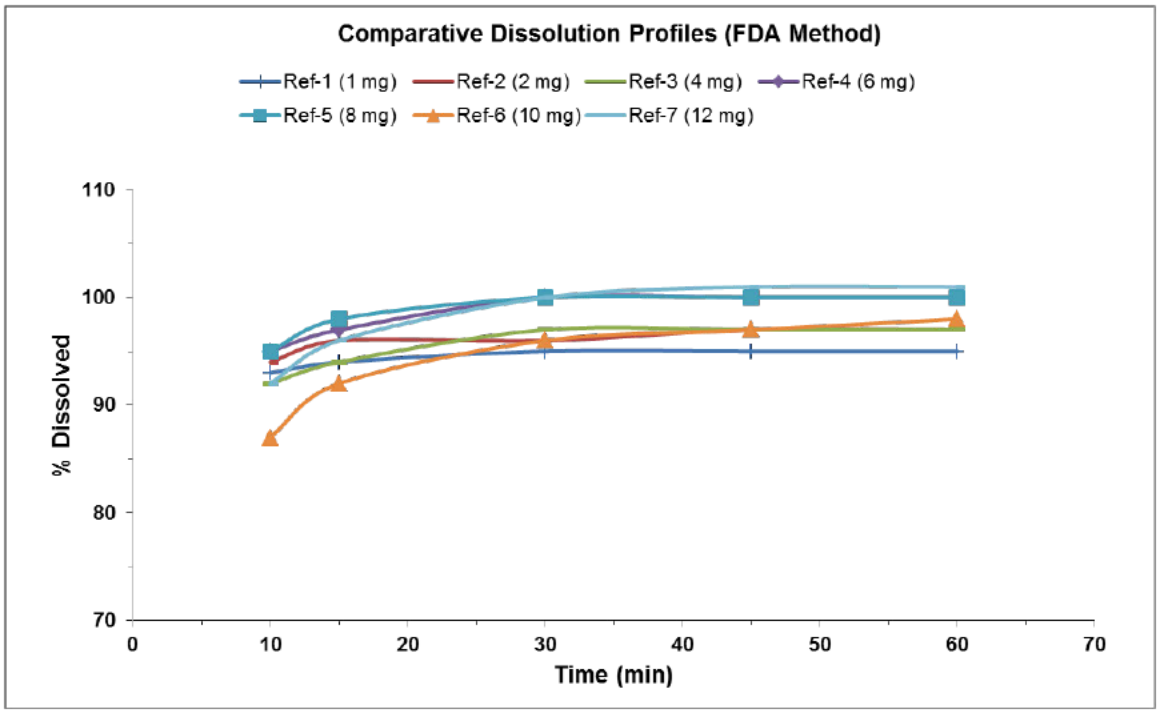
Dissolution Conditions	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N Hydrochloric acid
	Volume:	500 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)(4)% (Q) dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	INVENTIA HEALTHCARE PVT. LTD, Plot No.F1 & F-1/1, Additional MIDC, Ambernath (East)-421 506 District: Thane, Maharashtra, India	

Study Ref No.	Testing Date	Product ID (Test - Manufacture Date, Reference – Expiry Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (mins)					Study Report Location
						10	15	30	45	60	
Batch No. EXB/623/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg. date: Jul. 2013	10 mg Tablet	12	Mean	80	89	98	100	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.3	1.9	2.0	1.9	1.7	
Lot No. DXFY	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Apr. 2014	10 mg Tablet	12	Mean	87	92	96	97	98	Section 2.7.1.2
					Range	(b) (4)					
					% CV	2.5	1.3	1.0	0.7	1.0	
Batch No. EXB/624/01	Nov. 2013	Test Product: Iloperidone Tablets Mfg. date: Jul. 2013	12 mg Tablet	12	Mean	82	89	98	100	100	Section 2.7.1.2
					Range	(b) (4)					
					% CV	4.4	2.5	2.8	2.5	2.8	
Lot No. KKTF	Nov. 2013	Reference Product: Fanapt® Iloperidone Tablets Exp. date: Dec. 2015	12 mg Tablet	12	Mean	92	96	100	101	101	Section 2.7.1.2
					Range	(b) (4)					
					% CV	1.5	1.7	1.6	1.2	1.4	

Dissolution Profiles







F2 metric calculated?	☒ Yes ☒ No
If no, reason why F2 not calculated	Fast dissolving

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

Overall Comments: Adequate

Dissolution data were reviewed separately, and the overall review result is **adequate**[20]. Per the dissolution review, the DB II acknowledges that the firm will conduct the dissolution testing for its test product using the following FDA-recommended 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

[20] ANDA-207231-ORIG-1, http://panorama.fda.gov/task/view?ID=542129670039f143f84ce04856b9c61f, Biopharmaceutics Primary Review (completion date 14-Mar-2015 and 22-Jun-2015)

The dissolution data are adequate with respect to supporting waiver requests of the lower strengths.

4.4 Attachments

4.4.1 Additional Studies (If applicable)

Are there any additional studies? (e.g. pilot , failed) **If yes, please provide the location of report (complete/summary)**	☒ Yes ☐ No The firm also submitted 3 pilot studies located in Section 5.3.1.2, Pilot fasting Study H029-12, Pilot fed study H030-12, Pilot fasting Study H031-12. Please see Bioequivalence Summary table.

4.4.1.1 Pilot fasting study H029-12

Number of Subjects (N)	N = 8
Are the test formulations in the pilot/failed studies and pivotal studies similar[21]?	☒ Yes ☐ No Batch No: ILOT-1-1208045 was used in pilot studies# H029-12 and H030-12. The formulation is similar to that of the pivotal biobatch. The formulation data are attached below.
What was the objective of pilot/failed study?	To determine the single-dose oral bioequivalence of Iloperidone Tablets (2 x1 mg) of Inventia Healthcare Pvt Ltd., India and FANAPT® (iloperidone) tablets (2x1 mg) (b) (4) [redacted] Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 in normal, healthy, adult, human subjects under fasting condition.
Please comment on reason(s) of failure	LnCmax failed to meet the acceptable BE criteria of 80-120% under fasting conditions. It is mainly due to small number of subjects enrolled, therefore the power of the BE study is inadequate.
Any serious adverse events or deaths reported?	☐ Yes ☒ No

Iloperidone (Pilot study H029-12)

Iloperidone Tablets (No. of subjects completed =08)
Dose: 2 x 1 mg
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fasting Bioequivalence Study (Study No. H029-12)

Parameters	Test	N	RLD	N	Ratio	90% CI
$AUC_{0\text{-}INF}$	28647.878	8	29803.952	8	96.12	88.34-104.58
$AUC_{0\text{-}t}$	27034.783	8	28306.418	8	95.51	88.02-103.64
C_{max}	1985.282	8	2329.339	8	85.23	73.38-99.00

[21] Submission of Summary Bioequivalence Data for Abbreviated New Drug Applications

(b) (4)

4.4.1.2 Pilot fed study H030-12

Number of Subjects (N)	N = 11
Are the test formulations in the pilot/failed studies and pivotal studies similar[22]?	☒ Yes ☐ No Batch No: ILOT-1-1208045 was used in pilot studies# H029-12 and H030-12. The formulation is similar to that of the pivotal biobatch. The formulation data are attached below.
What was the objective of pilot/failed study?	To determine the single-dose oral bioequivalence of Iloperidone Tablets (2 x1 mg) of Inventia Healthcare Pvt Ltd., India and FANAPT® (iloperidone) tablets (2x1 mg) (b) (4) Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 in normal, healthy, adult, human subjects under fed condition.
Please comment on reason(s) of failure	LnCmax failed to meet the acceptable BE criteria of 80-120% under fed conditions. It is mainly due to small number of subjects enrolled, therefore the power of the BE study is inadequate. The calculated power and ISCV indicated larger intra-subject variability (36.9%) for PK parameter Cmax in the fed study, compared to that of the fasting study (15.0%), suggesting larger number of subjects be considered to achieve adequate power.
Any serious adverse events or deaths reported?	☐ Yes ☒ No

[22] Submission of Summary Bioequivalence Data for Abbreviated New Drug Applications

Iloperidone (Pilot Study H030-12)

Iloperidone Tablets (No. of subjects completed =11)
Dose: 2 x 1 mg
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fed Bioequivalence Study (Study No. H030-12)

Parameters	Test	N	RLD	N	Ratio	90% CI
$AUC_{0\text{-}INF}$	30021.498	11	27753.930	11	108.17	96.73-120.97
$AUC_{0\text{-}t}$	27771.21	11	25861.732	11	107.38	96.50-119.49
C_{max}	1412.464	11	1553.272	11	90.93	68.69-120.39

(b) (4)

[redacted]

4.4.1.3 Pilot fasting study H031-12

Number of Subjects (N)	N = 10
Are the test formulations in the pilot/failed studies and pivotal studies similar[23]?	☒ Yes ☐ No Batch No: SC0270 was used in pilot study# H031-12. The formulation is same as that of the pivotal biobatch. The formulation data are attached below.
What was the objective of pilot/failed study?	To determine the single-dose oral bioequivalence of Iloperidone Tablets (2 x 1 mg) of Inventia Healthcare Pvt Ltd., India and FANAPT® (iloperidone) tablets (2x1 mg) (b) (4) [redacted] Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 in normal, healthy, adult, human subjects under fasting condition.
Please comment on reason(s) of failure	LnCmax failed to meet the upper bound of BE criteria of 80-125% under fasting conditions. It is mainly due to small number of subjects enrolled, therefore the power of the BE study is inadequate.
Any serious adverse events or deaths reported?	☐ Yes ☒ No

[23] Submission of Summary Bioequivalence Data for Abbreviated New Drug Applications

Iloperidone (Pilot Study H031-12)

Iloperidone Tablets (No. of subjects completed =10)
Dose: 2 x 1 mg
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fasting Bioequivalence Study (Study No. H031-12)

Parameters	Test	N	RLD	N	Ratio	90% CI
$AUC_{0\text{-}INF}$	22772.386	10	23044.764	10	98.82	88.30-110.59%
$AUC_{0\text{-}t}$	20785.952	10	20817.820	10	99.85	91.41-109.06%
C_{max}	1426.064	10	1296.286	10	110.01	89.76-134.83%

(b) (4)

4.4.2 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Table
Fasting	207231_FASTING_Datasets_Iloperidone.(	Fasting 207231_iloperidone_(	207231_FASTING_stat_Iloperidone.doc	207231_FASTING_table_Iloperidone.doc
	207231_FASTING_Datasets_P88.doc	Fasting 207231_p88_CONTIN	207231_FASTING_stat_P88.doc	207231_FASTING_table_P88.doc
Fed	207231_FED_Datasets_Iloperidone.doc	Fed 207231_iloperidone_(	207231_FED_stat_Iloperidone.doc	207231_FED_table_Iloperidone.doc
	207231_FED_Datasets_P88.doc	Fed 207231_p88_CONTIN	207231_FED_stat_P88.doc	207231_FED_table_P88.doc

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 207231

APPLICANT: Inventia Healthcare Private Limited

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

The Division of Bioequivalence 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}

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