CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 207098

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

Sponsor: Taro Pharmaceutical Industries Limited

Approval Date: July 22, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA208891Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207098

APPROVAL LETTER

ANDA 207098

ANDA APPROVAL

Taro Pharmaceuticals U.S.A. Inc.
U.S. Agent for Taro Pharmaceutical Industries Limited
3 Skyline Drive
Hawthorne, NY 10532
Attention: Crystal Spinks, Ph.D.
Senior Manager, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 2, 2014, 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 complete response letter issued by this office on February 22, 2019, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug 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).

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

U.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

With respect to the '638, '742, '254, '255, '256, '432, and '121 patents,[1] your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Iloperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg, under this ANDA. You have notified the Agency that Taro Pharmaceutical Industries Limited complied with the requirements of section 505(j)(2)(B) of the FD&C Act.

With respect to the '610 and '776 patents, the Agency has determined that information on these patents was submitted to the Agency by the new drug application (NDA) holder (a) after the date of the submission of your ANDA, and (b) more than 30 days after the patent was required to be submitted under 21 CFR 314.53. Therefore, under 21 CFR 314.94(a)(12)(vi), no person with an appropriate patent certification at the time of the submission of the patent was required to submit an amended patent certification to address the '610 and '776 patents. You elected not to submit an amended patent certification with respect to these patents.

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

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

REPORTING REQUIREMENTS

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[2] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts.

All finished dosage forms (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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Vincent Sansone, PharmD
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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

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

Vincent Sansone

Digitally signed by Vincent Sansone
Date: 7/22/2019 12:42:06PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207098

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ILOPERIDONE tablets, 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----------

Boxed Warning	5/2016
Indications and Usage (1)	5/2016
Dose and Administration (2.3)	5/2016
Warnings and Precautions (5.1, 5.2)	5/2016
Warnings and Precautions (5.3, 5.9)	2/2017

----------INDICATIONS AND USAGE----------

Iloperidone is an atypical antipsychotic indicated for the treatment of schizophrenia in adults. (1, 14) In choosing among treatments, prescribers should consider the ability of iloperidone to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate iloperidone slowly to avoid orthostatic hypotension, which may lead to delayed or even slow compared to some other drugs that do not require similar titration. (2.1, 14)

----------DOSAGE AND ADMINISTRATION----------

The recommended target dosage of iloperidone tablets is 12 mg/day 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 tablets 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 tablets in combination with other drugs that are known to prolong QTc; use caution and consider dose modification when prescribing iloperidone tablets with other drugs that inhibit iloperidone metabolism. Monitor serum potassium and magnesium in patients at risk for electrolyte disturbances. (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 tablets at the first sign of a decline in WBC in the absence of other causative factors. (5.10)
- Suicide: Close supervision of high risk patients. (5.14)
- Priapism: Cases have been reported in association with iloperidone tablet treatment. (5.15)
- Potential for cognitive and motor impairment: Use caution when operating machinery. (5.16)

----------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 Teva Pharmaceuticals U.S.A., Inc. at 1-866-923-4914 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

The dose of iloperidone tablets should be reduced in patients coadministered 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)
- Lactation: Advise not to breast feed. (8.2)
- Pediatric Use: Safety and effectiveness not established in children and adolescents. (8.4)
- Hepatic impairment: Iloperidone tablets are not recommended for patients with severe hepatic impairment. (2.2, 8.6)
- The dose of iloperidone tablets should be reduced in patients who are poor metabolizers of CYP2D6. (2.2, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Issued: 03/2018

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 tablets are 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 treated 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 tablets must be titrated slowly from a low starting dose to avoid orthostatic hypotension due to its alpha-adrenergic blocking properties. The recommended starting dose for iloperidone tablets is 1 mg orally twice daily. Dose increases to reach the target range of 6 mg to 12 mg twice daily (12 mg/day 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 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 mg to 12 mg twice daily. Prescribers should be mindful of the fact that patients need to be titrated to an effective dose of iloperidone tablets. Thus, control of symptoms may be delayed during the first 1 week 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 tablet 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 tablets concomitantly with potential CYP2D6 inhibitors: Iloperidone tablet 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 tablet dose should then be increased to where it was before *[see Drug Interactions (7)]*.

Dosage adjustment for patients taking iloperidone tablets concomitantly with potential CYP3A4 inhibitors: Iloperidone tablet 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 tablet dose should be increased to where it was before *[see Drug Interactions (7)]*.

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

Hepatic Impairment: No dose adjustment to iloperidone tablets is needed in patients with mild hepatic impairment. Patients with moderate hepatic impairment may require dose reduction, if clinically indicated. Iloperidone tablets are not recommended for patients with severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

2.3 Maintenance Treatment

In a long-term study, iloperidone tablets were effective in delaying time to relapse in patients with schizophrenia who were stabilized on iloperidone tablets up to 24 mg/day *[see Clinical Studies (14)]*. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.4 Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that the initiation titration schedule be followed whenever patients have had an interval 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 oval (1 mg) white tablets are engraved with "T" on one side and on the other side the tablet strength. The round (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg) white tablets are engraved with "T" on one side and on the other side the tablet strength.

4 CONTRAINDICATIONS

Iloperidone tablets are 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 times 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 tablets are 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 19 msec at an iloperidone dose of 12 mg twice daily. The effect of iloperidone on the QT interval was suppressed 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 tablets 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 tablets should also be avoided in patients with a known genetic susceptibility to 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 tablets 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 tablet 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 tablets 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 tablets should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

If patients taking iloperidone tablets 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, heatstroke, 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 upon 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 tablets 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 drugs less likely to be effective, and 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 tablets, drug discontinuation should be considered. However, some patients may require treatment with iloperidone tablets 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 tablets. 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)		
	n=114	n=228
Serum Glucose Change from Baseline	-0.5	8.6
Proportion of Patients with Shifts		
Serum Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	2.5% (2/80)	10.7% (18/168)

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 months to 6 months	6 months to 12 months	>12 months
Iloperidone tablets 10 mg/day to 16 mg/day	1.9 (N=773)	5.4 (N=723)	5.4 (N=425)
Iloperidone tablets 20 mg/day to 24 mg/day	-3.6 (N=34)	-9 (N=31)	-18 (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	-0.93
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)	23.9% (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 Table 4 and Table 5.

Table 4: Change in Cholesterol

	Mean Change from Baseline (mg/dL)		
	3 months to 6 months	6 months to 12 months	>12 months
Iloperidone tablets 10 mg/day to 16 mg/day	-3.9 (N=783)	-3.9 (N=726)	-7.7 (N=428)
Iloperidone tablets 20 mg/day 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 months to 6 months	6 months to 12 months	>12 months
Iloperidone tablets 10 mg/day to 16 mg/day	-6.9 (N=79.3)	-6.9 (N=7.26)	-17.7 (N=426)
Iloperidone tablets 20 mg/day to 24 mg/day	-26.6 (N=3.4)	-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-week 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 mg/day to 16 mg/day n=481	Iloperidone Tablets 20 mg/day to 24 mg/day n=391
Weight (kg) Change from Baseline	-0.1	2	2.7
Weight Gain ≥7% Increase from Baseline	4%	12%	18%

5.7 Seizures

In short-term placebo-controlled trials (4-weeks to 6-weeks), seizures occurred in 0.1% (1/1344) of patients treated with iloperidone tablets compared to 0.3% (2/587) on placebo. As with other antipsychotics, iloperidone tablets 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 tablets 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% (5/1344) of patients treated with iloperidone tablets, compared with 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 5% of patients given 20 mg/day to 24 mg/day, 3% of patients given 10 mg/day 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 tablets 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 Falls

Iloperidone tablets may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.10 Leukopenia, Neutropenia and Agranulocytosis

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

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

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue iloperidone and have their WBC followed until recovery.

5.11 Hyperprolactinemia

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

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis 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 tablets *[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 in patients with schizophrenia, 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 tablets compared to 12% in the placebo group. In the short-term trials, iloperidone was associated with modest levels of prolactin elevation compared to greater prolactin elevations observed with some other antipsychotic agents. In pooled analysis from clinical studies including longer term trials, in 3210 adults treated with iloperidone, gynecomastia was reported in 2 male subjects (0.1%) compared to 0% in placebo-treated patients, and galactorrhea was reported in 8 female subjects (0.2%) compared to 0% in placebo-treated patients.

5.12 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 tablets 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.

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

5.14 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 tablets should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

5.15 Priapism

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

5.16 Potential for Cognitive and Motor Impairment

Iloperidone tablets, 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 tablets 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 tablets 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 tablets consisting of 3229 patients exposed to iloperidone tablets at doses of 10 mg/day or greater, for the treatment of schizophrenia. Of these, 999 received iloperidone tablets for at least 6 months, with 657 exposed to iloperidone tablets for at least 12 months. All of these patients who received iloperidone tablets were participating in multiple-dose clinical trials. The conditions and duration of treatment with iloperidone tablets varied greatly and included (in one study or combining studies) 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-week or 6-week, fixed- or flexible-dose studies in patients who received iloperidone tablets 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 Tablet-Treated Patients and More Frequent than in Placebo

Table 7 enumerates the pooled incidences of adverse reactions that were spontaneously reported in four placebo-controlled, 4-week or 6-week, fixed- or flexible-dose studies, listing those reactions that occurred in 2% or more of patients treated with iloperidone tablets in any of the dose groups, and for which the incidence in iloperidone tablet-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 / Dictionary-Derived Term	Placebo % (N=587)	Iloperidone Tablets 10 mg/day to 16 mg/day % (N=483)	Iloperidone Tablets 20 mg/day to 24 mg/day % (N=391)
Body as a Whole			
Asthenia	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	6	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-week or 6-week, fixed- or flexible-dose studies, adverse reactions that occurred with a greater than 2% incidence in the patients treated with iloperidone tablets, and for which the incidence in patients treated with iloperidone tablets 24 mg/day to 24 mg/day were twice than the incidence in patients treated with iloperidone tablets 10 mg/day 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-week or 6-week, fixed- or flexible-dose studies, the following adverse reactions occurred in ≥5% incidence in the patients treated with iloperidone tablets 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 mg/day to 24 mg/day as on 10 mg/day to 16 mg/day.

Extrapyramidal Symptoms (EPS) in Clinical Trials

Pooled data from the 4 placebo-controlled, 4-week 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 mg/day to 16 mg/day (%) (N=483)	Iloperidone Tablets 20 mg/day 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
Dystonia	0.7	1	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-week or 6-week, fixed- or flexible-dose studies, there was no difference in the incidence of discontinuation due to adverse events between iloperidone tablet-treated (5%) and placebo-treated (5%) patients. The types of adverse events that led to discontinuation were similar for the iloperidone tablet- and placebo-treated patients.

Demographic Differences in Adverse Reactions in Clinical Trials

An examination of population subgroups in the 4 placebo-controlled, 4-week 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 tablets and placebo in the incidence of discontinuation due to changes in hematology, urinalysis, or serum chemistry.

In short-term placebo-controlled trials (4-weeks to 6-weeks), there were 1% (13/1342) iloperidone-treated patients with hematocrit at least one time below the extended normal range during post-randomization treatment, compared to 0.3% (2/585) on placebo. The extended normal range for lowered hematocrit was defined in each of these trials as the value 15% below the normal range for the centralized laboratory that was used in the trial.

Other Reactions During the Pre-marketing Evaluation of Iloperidone Tablets

The following is a list of MedDRA terms that reflect adverse reactions in patients treated with iloperidone tablets at multiple doses ≥ 4 mg/day during any phase of a trial with the database of 3210 iloperidone tablet-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 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic Disorders: Infrequent – anemia, iron deficiency anemia; *Rare* – leukopenia

Cardiac Disorders: Frequent – palpitations; *Rare* – arrhythmia, atrioventricular block first degree, cardiac failure (including congestive and acute)

Ear and Labyrinth Disorders: Infrequent – vertigo, tinnitus

Endocrine Disorders: Infrequent – hypothyroidism

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

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

General Disorders and Administrative Site Conditions: Infrequent – edema (general, pitting, due to cardiac disease), difficulty in walking, thirst; *Rare* – hyperthermia

Hepatobiliary Disorders: Infrequent – cholelithiasis

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

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

Musculoskeletal and Connective Tissue Disorders: Frequent – myalgia, muscle spasms; *Rare* – torticollis

Nervous System Disorders: Infrequent – paresthesia, psychomotor hyperactivity, restlessness, amnesia, nystagmus; *Rare* – restless legs syndrome

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

Renal and Urinary Disorders: Frequent – urinary incontinence; *Infrequent* – dysuria, pollakiuria, enuresis, nephrolithiasis; *Rare* – urinary retention, renal failure acute

Reproductive System and Breast Disorders: Frequent – erectile dysfunction; *Infrequent* – testicular pain, amenorrhea, breast pain; *Rare* – menstruation irregular, gynecomastia, menorrhagia, metrorrhagia, postmenopausal hemorrhage, prostatitis.

Respiratory, Thoracic and Mediastinal Disorders: Infrequent – epistaxis, asthma, rhinorrhea, sinus congestion, nasal dryness; *Rare* – dry throat, sleep apnea syndrome, dyspnea exertional

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of iloperidone tablets: 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 tablets, 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 tablets have the potential to enhance the effect of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect Iloperidone Tablets

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: Coadministration 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 years 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: Coadministration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29 years to 44 years, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2-fold 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 days to 8 days), a potent inhibitor of CYP2D6, with multiple doses of iloperidone (8 mg or 12 mg twice daily) to patients with schizophrenia ages 18 years 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 mg or 12 mg twice daily) to patients with schizophrenia ages 18 years 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 Tablets 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 coadministered 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 CYP3A4 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 tablets 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 tablets, 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 tablets 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/m² 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/m² 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 mg/kg/day, 16 mg/kg/day, or 64 mg/kg/day (1.6 times, 6.5 times, and 26 times the maximum recommended human dose (MRHD) of 24 mg/day on a mg/m² 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 mg/kg/day, 10 mg/kg/day, or 25 mg/kg/day (3 times, 8 times, and 20 times the MRHD on a mg/m² 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 mg/kg 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/m² 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 mg/kg/day, 80 mg/kg/day, 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 tablets.

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.

8.3 Pediatric Use

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

8.4 Geriatric Use

Clinical Studies of iloperidone tablets in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 years and over to determine whether or not they respond differently than younger adult patients. Of the 3210 patients treated with iloperidone tablets 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 tablets are at an increased risk of death compared to placebo. Iloperidone tablets are not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1, 5.2)]*.

8.5 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.

8.6 Hepatic Impairment

No dose adjustment to iloperidone tablets is needed in patients with mild hepatic impairment. Patients with moderate hepatic impairment may require dose reduction. Iloperidone tablets are 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 tablets are not recommended for patients with severe hepatic impairment.

8.7 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 tablet misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In pre-marketing trials involving over 3210 patients, accidental or intentional overdose of iloperidone tablets 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 tablet 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.

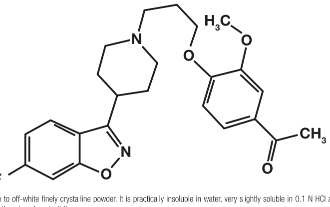
10.2 Management of Overdose

There is no specific antidote for iloperidone tablets. 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 antipsychotic 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 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, and purified water (removed during processing). The oval (1 mg) white tablets are engraved with "T" on one side and on the other side the tablet strength. The round (2 mg, 4 mg, 6 mg, 8 mg, 10 mg or 12 mg) white tablets are engraved with "T" on one side and on the other side the tablet strength.

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 ($5\text{-}HT_2$) 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 $5\text{-}HT_{2A}$ dopamine D_2 and D_3 receptors, and norepinephrine $NE_{\alpha1}$ receptors (K_i values of 5.6 nM, 6.3 nM, 7.1 nM, and 0.36 nM, respectively). Iloperidone has moderate affinity for dopamine D_4, and serotonin $5\text{-}HT_6$ and $5\text{-}HT_7$ receptors (K_i values of 25 nM, 43 nM, and 22 nM respectively), and low affinity for the serotonin $5\text{-}HT_{1A}$, dopamine D_1, and histamine H_1 receptors (K_i values of 168 nM, 216 nM and 437 nM, respectively). Iloperidone has no appreciable affinity (K_i>1000 nM) for cholinergic muscarinic receptors. The affinity of the iloperidone metabolite P88 is generally equal to or less than that of the parent compound, while the metabolite P95 only shows affinity for $5\text{-}HT_{2A}$ (K_i value of 3.91) and the $NE_{\alpha1A}$, $NE_{\alpha1B}$, $NE_{\alpha1D}$, and $NE_{\alpha2C}$ receptors (K_i values of 4.7 nM, 2.7 nM, 8.8 nM 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 hours, 26 hours and 23 hours, respectively, and in poor metabolizers (PM) are 33 hours, 37 hours and 31 hours, respectively. Steady-state concentrations are attained within 3 days 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 hours 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 tablets can be administered without regard to meals.

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

Metabolism and Elimination: Iloperidone is metabolized primarily by 3 biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and *O*-demethylation (mediated by CYP3A4). There are 2 predominant iloperidone metabolites, P95 and P88. The iloperidone metabolite P95 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34% of total plasma exposure in EM and PM, respectively.

Approximately 7% to 10% of Caucasians and 3% to 8% of Black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive or ultrarapid metabolizers. Coadministration of iloperidone tablets 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 tablet 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 mg/kg/day, 5 mg/kg/day and 10 mg/kg/day to CD-1 mice and 4 mg/kg/day, 8 mg/kg/day and 16 mg/kg/day to Sprague Dawley rats (0.5 times, 1 time and 2 times and 1.6 times, 3.2 times and 6.5 times, respectively, the MRHD of 24 mg/day on a mg/m² basis). There was an increased incidence of malignant mammary gland tumors in female mice treated with the lowest dose (2.5 mg/kg/day) only. There were no treatment-related increases in neoplasia in rats.

The carcinogenic potential of the iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present at significant amounts in mice or rats, was assessed in a lifetime carcinogenicity study in Wistar rats at oral doses of 25 mg/kg/day, 75 mg/kg/day and 200 mg/kg/day in males and 50 mg/kg/day, 150 mg/kg/day 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 mg/kg/day, 75 mg/kg/day, and 200 mg/kg/day) were approximately 0.4 times, 3 times, 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 mg/kg 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/m² basis.

14 CLINICAL STUDIES

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

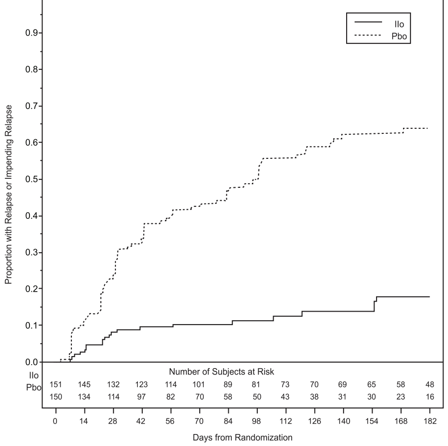
Three instruments were used for assessing psychiatric signs and symptoms in these studies. The Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia. The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

A 6-week, placebo-controlled trial (n=706) involved 2 flexible dose ranges of iloperidone (12 mg/day to 16 mg/day or 20 mg/day to 24 mg/day) compared to placebo and an active control (risperidone). For the 12 mg/day to 16 mg/day group, the titration schedule of iloperidone tablets 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 mg/day to 24 mg/day group, the titration schedule of iloperidone tablets 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 mg/day to 16 mg/day and the 20 mg/day to 24 mg/day dose ranges of iloperidone tablets were superior to placebo on the BPRS total score. The active control antipsychotic drug appeared to be superior to iloperidone tablets 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 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg twice daily on Days 2, 3, 4, 5, 6, and 7. The primary endpoint was change from baseline on the PANSS total score at the end of treatment (Day 28). The 24 mg/day iloperidone dose was superior to placebo in the PANSS total score. Iloperidone tablets appeared to have similar efficacy to the active control drug which also needed a slow titration to the target dose.

In a longer-term trial, clinically stable adult outpatients (n=303) meeting DSM-IV criteria for schizophrenia who remained stable following 12 weeks of open-label treatment with flexible doses of iloperidone (8 mg/day to 24 mg/day administered as twice daily doses) were randomized to placebo or to continue on their current iloperidone dose (8 mg/day to 24 mg/day administered as twice daily doses) for observation for possible relapse during the double-blind relapse prevention phase. Stabilization during the open-label phase was defined as being on an established dose of iloperidone that was unchanged due to efficacy in the 4 weeks prior to randomization, having CGI-Severity score of ≤4 and PANSS total score ≤70, a score of ≤4 on each of the following individual PANSS items (P1-delusions, P2-conceptual disorganization, P3-hallucinatory behavior, P6-suspiciousness/persecution, P7-hostility, or G8-uncooperativeness), and no hospitalization or increase in level of care to treat exacerbations. Relapse or impending relapse during the double-blind relapse prevention phase was defined as any of the following: hospitalization due to worsening of schizophrenia, increase (worsening) of the PANSS total score ≥30%, CGI-Improvement score ≥6, patient had suicidal, homicidal, or aggressive behavior, or need for any other antipsychotic medication.

Figure 1: Kaplan Meier Estimation of Percent Relapse/Impending Relapse for Iloperidone (Ilo) and Placebo (Pbo)



Based on the interim analysis, an independent data monitoring committee decided the study should be discontinued early due to evidence of efficacy. Based on results from the interim analysis, which were confirmed by the final analysis dataset, patients treated with iloperidone tablets experienced a statistically significant longer time to relapse or impending relapse than patients who received placebo. Figure 1 displays the estimated cumulative proportion of patients with relapse or impending relapse based on the final data set.

16 HOW SUPPLIED/STORAGE AND HANDLING

Iloperidone tablets are available in the following strengths: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. The oval (1 mg) white tablets are engraved with "T" on one side and on the other side the tablet strength. The round (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg) white tablets are engraved with "T" on one side and on the other side the tablet strength. Tablets are supplied in the following package configurations:

Package Configuration	Tablet Strength (mg)	NDC Number
Bottles of 60	1 mg	51672-4178-4
Bottles of 60	2 mg	51672-4179-4
Bottles of 60	4 mg	51672-4180-4
Bottles of 60	6 mg	51672-4181-4
Bottles of 60	8 mg	51672-4182-4
Bottles of 60	10 mg	51672-4183-4
Bottles of 60	12 mg	51672-4184-4
Titration Pack	2x1 mg, 2x2 mg, 2x4 mg, 2x6 mg (Total of 8 tablets)	51672-4213-7

Storage

Store at 20° to 25°C (68° to 77°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 therapy does not affect them adversely *[see Warnings and Precautions (5.16)]*.

Pregnancy

Advise patients that third trimester use of iloperidone tablets 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)]*.

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)]*.

Lactation

Advise women not to breastfeed during treatment with iloperidone tablets *[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.

Mfd. by: Taro Pharmaceutical Industries Ltd., Haifa Bay, Israel 2624761
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.,** Hawthorne, NY 10532
Issued: March 2018 20670-0318-0

NDC 51672-4178-4 60 Tablets

Iloperidone Tablets 1 mg

Keep this and all medications out of the reach of children.

Rx only

Each tablet contains: 1 mg iloperidone

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from light and moisture.

N 3 51672 41784 0

Mfd. by: Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 2624761
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**
Hawthorne, NY 10532
TARO is a registered trademark of
Taro Pharmaceuticals U.S.A., Inc.
20671-1115-0

NDC 51672-4179-4

60 Tablets

Iloperidone Tablets 2 mg

Keep this and all medications out of the reach of children.

Rx only

Each tablet contains: 2 mg iloperidone

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from light and moisture.

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Haifa Bay, Israel 2624761

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Hawthorne, NY 10532

20672-1115-0

3 N 51672417949 9

TARO

NDC 51672-4180-4

60 Tablets

Iloperidone Tablets 4 mg

Keep this and all medications out of the reach of children.

Rx only

Each tablet contains: 4 mg iloperidone

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from light and moisture.

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Hawthorne, NY 10532

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20673-1115-0

TARO

NDC 51672-4181-4

60 Tablets

Iloperidone Tablets 6 mg

Keep this and all medications out of the reach of children.

Rx only

Each tablet contains: 6 mg iloperidone

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from light and moisture.

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20674-1115-0

3 N 51672 4181 4 4

TARO

TARO

NDC 51672-4182-4 60 Tablets

Iloperidone Tablets 8 mg

Keep this and all medications out of the reach of children.

Rx only

Each tablet contains: 8 mg iloperidone
Usual Dosage: See package insert for full prescribing information.
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Protect from light and moisture.

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Hawthorne, NY 10532

20675-1115-0

NDC 51672-4183-4

60 Tablets

Iloperidone Tablets 10 mg

Keep this and all medications out of the reach of children.

Rx only

Each tablet contains: 10 mg iloperidone

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from light and moisture.

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Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

20676-1115-0

N 3 51672 41834 2

TARO

TARO

NDC 51672-4184-4

60 Tablets

Iloperidone Tablets 12 mg

Keep this and all medications out of the reach of children.

Rx only

Each tablet contains: 12 mg iloperidone

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from light and moisture.

20677 -1115-0

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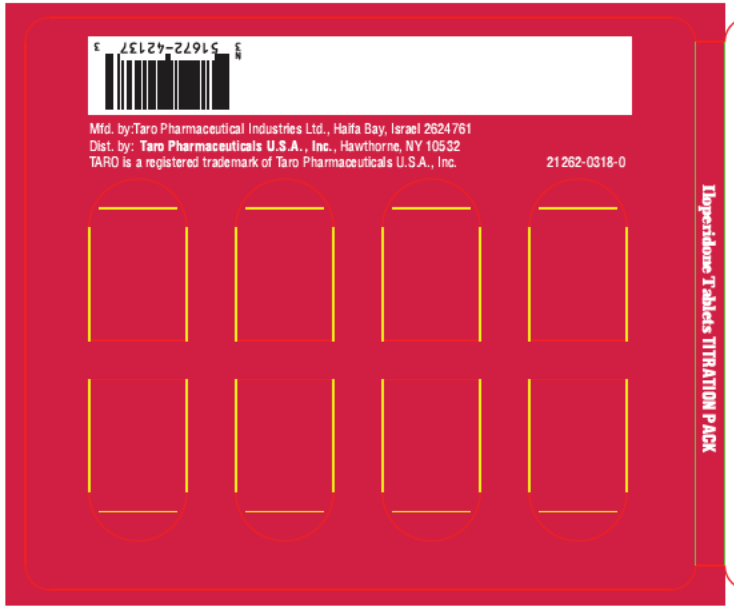
Hawthorne, NY 10532



HOW TO BEGIN THERAPY WITH ILOPERIDONE TABLETS

Take one tablet by mouth twice daily according to the schedule shown on the panel to the right. Once you have completed this initial course, continue taking iloperidone tablets as directed by your physician.

SPECIAL INSTRUCTIONS FROM YOUR HEALTH CARE PROVIDER

_____

_____

_____

DOSAGE INSTRUCTIONS:

DAY 1	DAY 2	DAY 3	DAY 4
Take one 1-mg tablet in the morning (AM), and one 1-mg tablet in the evening (PM)	Take one 2-mg tablet in the morning (AM), and one 2-mg tablet in the evening (PM)	Take one 4-mg tablet in the morning (AM), and one 4-mg tablet in the evening (PM)	Take one 6-mg tablet in the morning (AM), and one 6-mg tablet in the evening (PM)
Morning	Morning	Morning	Morning
1 mg	2 mg	4 mg	6 mg
1 mg	2 mg	4 mg	6 mg
Evening	Evening	Evening	Evening

(b) (4)

100MM

100MM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207098

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

TEMPLATE 2 (SIMPLE IMMEDIATE RELEASE PRODUCTS)

ANDA No.	207098		
Drug Product Name	Iloperidone Tablets		
Strength(s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg		
Applicant Name	Taro Pharmaceutical U.S.A., Inc.		
Applicant Address	3 Skyline Drive Hawthorne, NY 10532		
Contact	Kavita Srivastava		
US agent's Telephone Number	914 345 9001 (b) (6)		
US Agent's Fax Number	914 593 0078		
US Agent's Email Address	Kavita.srivastava@taro.com		
Original Submission Date(s)	06/02/2014		
Submission Date(s) of Amendment(s) Under Review	05/29/2015 Multiple Categories/Subcategories		
Reviewer	Yang Chang, Pharm.D., Ph.D.		
Study Number (s)	PKD_13_459	PKD_13_460	2013-3306
Study Type (s)	Pivotal Fasting	Pivotal Fed	Pilot Fasting
Strength (s)	1 mg	1 mg	1 mg
Clinical Site	Sun Pharmaceutical Industries Ltd		Pharma Medica Research Inc.
Clinical Site Address	Clinical Pharmacology Unit, Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (India)		4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6
Analytical Site	(b) (4)		
Analytical Site Address			
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete**	**Year 3 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**	
OVERALL REVIEW RESULT	**Adequate**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
COMMUNICATION	☐ **ECD** ☐ **IR**		

	☒ NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
#1 and #4	**Fasting**	**1 mg**	**Adequate**
#1 and #4	**Fed**	**1 mg**	**Adequate**
#1 and #4	**Waiver**	**2 mg**	**Adequate**
#1 and #4	**Waiver**	**4 mg**	**Adequate**
#1 and #4	**Waiver**	**6 mg**	**Adequate**
#1 and #4	**Waiver**	**8 mg**	**Adequate**
#1 and #4	**Waiver**	**10 mg**	**Adequate**
#1 and #4	**Waiver**	**12 mg**	**Adequate**

1. EXECUTIVE SUMMARY

This is a review of an amendment dated May 29, 2015.

Based on the original bioequivalence (BE) review, the firm's pivotal fasting and fed studies are adequate. The formulations for the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths are proportionally similar to the 1 mg strength of the test product which underwent bioequivalence testing. The OSIS inspection status of this application is complete.[1] However, the application was inadequate due to the deficiencies related to the details of the adverse events in the pilot study and inadequate dissolution data submitted in support of waiver requests. The firm was contacted through information request (IR) on April 27, 2015 regarding the above deficiencies.[2]

The current amendment contains the firm's response to the deficiencies. The Division of Bioequivalence III (DBIII) finds the firm's response **acceptable**. The dissolution data is adequate with respect to supporting waiver requests of the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg strengths of the test product.

As a result, the application is now **adequate**.

[1] GDRP, ANDA-207098-ORIG-1, Bioequivalence Primary Review, Date Uploaded May 3, 2015
[2] GDRP, ANDA-207098-ORIG-1, Bioequivalence Primary Review, Email_ANDA_207098_2015-05-04 03_23_37.zip

2. TABLE OF CONTENTS

3. BACKGROUND

In the original submission, Taro Pharmaceutical U.S.A., Inc. submitted in vivo fasting and fed BE studies comparing its 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 pivotal fasting and fed BE studies are adequate. However, the application was inadequate due to the deficiencies related to the adverse events' clarification in the pilot study and dissolution data. The firm was contacted through information request (IR) on April 27, 2015 regarding the above deficiencies.

In the current amendment dated May 29, 2015, the firm provided its response to IR.

4. CONTENTS OF SUBMISSION

Study Types	Yes/No?	How many?
Single-dose fasting (Pivotal)	-	-
Single-dose fed	-	-
Steady-state	-	-
Single-dose fasting and fed (Pilot)	-	-
In vitro dissolution	-	-
Waiver requests	-	-
BCS Waivers	-	-
Clinical Endpoints	-	-
Failed Studies	-	-
Amendment	Yes	1

5. REVIEW OF CURRENT AMENDMENT

DBIII Deficiency Comment:
Please provide the details of all adverse events (AEs) reported in the pilot study (2013-3306) including the severity/intensity of the AEs (i.e., mild, moderate, severe, serious etc.).

Firm's Response to deficiency Comment:
Details of all adverse events (AEs) reported in the pilot study (2013-3306) including the severity/intensity of the AEs are provided in Module 5.3.1.2 under study folder 2013-3306 "ae-listing-study -2013-3306.pdf".

Reviewer's Comment on the Firm's Response to Deficiency Comment:

- The firm provided details of all AEs reported in the pilot study including the severity of the AEs. The relation of the AEs to the drugs were probable or

unlikely and the severity of all reported AEs were mild. There is no substantial difference between the test and reference product for adverse event profile. There are no other safety concerns based on the adverse event profile of the pilot study provided by firm.

- The firm's response to this deficiency comment is adequate.

DBIII Deficiency Comment:
Your waiver requests for the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg strengths are not considered at this time due to inadequate dissolution testing data for all strengths of the test and reference products. Your dissolution testing was conducted (b) (4) Please submit additional dissolution testing data on twelve (12) dosage units of unexpired batches of each test and reference product using the following FDA-recommended method (b) (4) to support the waiver requests of the lower strengths of the test product, as well to establish a regulatory dissolution method and specifications for quality control purposes.

Apparatus	II (paddle)
Speed of Rotation	50 rpm
Medium	0.1N HCl
Volume	500 mL
Recommended Sampling Times	5, 10, 15, 30, 45 and 60 minutes

Firm's Response to deficiency Comment:
Additional dissolution testing was conducted by Taro on twelve (12) dosage units of unexpired batches of each test and reference product using the recommended FDA method (b) (4) to support Taro's waiver requests of the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg strengths of the test product (please see individual dissolution testing data in Appendix).

Reviewer's Comment on the Firm's Response to Deficiency Comment:

- The firm conducted the dissolution testing on twelve (12) dosage units of unexpired batches of each test and reference product using the FDA-recommended method (b) (4)
- Each strength of the test product releases (b) (4) than (b) (4)% of iloperidone within 30 minutes, so the similarity factor (F2) calculation is not applicable.
- The dissolution data is adequate to support the waiver requests of the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg strengths of the test product.
- The firm's response to this deficiency comment is adequate.

DBIII Deficiency Comment:
If necessary, please develop a discriminating and reproducible dissolution method, using conventional USP apparatuses and vessels, for the purpose of comparing dissolution profiles between strengths of the test and reference products in support of your waiver requests of the lower strengths.

Firm's Response to deficiency Comment:
Since Taro will adopt the FDA-recommended method (with conventional USP dissolution vessels) for dissolution testing of its drug product Iloperidone Tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg, it is not necessary to develop a discriminating method at this time [redacted] (b) (4) is enclosed in Module 3.2.P.5.2.

Reviewer's Comment on the Firm's Response to Deficiency Comment:

- The firm conducted acceptable dissolution testing using the FDA-recommended method. The dissolution data is adequate to support the waiver requests of the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg strengths of the test product.
- The firm's response to this deficiency comment is adequate.

6. APPENDIX

Comment 1 in the IR letter (Dissolution Comment):
Your dissolution testing is not acceptable. [redacted] (b) (4)
Please conduct dissolution testing on twelve (1 2) dosage units of unexpired batches of each test and reference product using the following FDA-recommended method:

USP Apparatus	II (paddle)
Rotation speed	50 rpm
Medium	0.1N HCl
Volume	500 mL
Temperature	37 ± 0.5 °C
Sampling Times	5, 10, 15, 30, 45 and 60 minutes

Firm's response to comment No.1 (dissolution deficiency comment)
As per the Division of Bioequivalence request, Taro had conducted comparative dissolution testing of its lloperidone Tablets vs. the Reference Listed Drug (RLD) Fanapt® (IIoperidone) Tablets for all product strengths (1mg, 2mg, 4mg, 6mg, 8mg, 10mg, and 12mg). The dissolution testing was conducted according to the FDA recommended dissolution method as detailed above, [redacted] (b) (4)
Based on these dissolution results, Taro acknowledges the Agency's recommendation to use the FDA recommended method (Apparatus II (paddle); 50rpm, 0.1N HCl, 500 mL) [redacted] (b) (4) for testing dissolution at release and stability of its Iloperidone Tablets 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg. [redacted] (b) (4) The updated dissolution method is enclosed in Module 3.2.P.5.2.

[redacted] (b) (4)
Therefore, based on the data generated, Taro is proposing acceptance criteria of NLT

(b) (4)% (Q) in 30 minutes for the dissolution of its Iloperidone Tablets. The proposed specifications are enclosed in Module 3.2.P.5.1 and 3.2.P.8.1.

Dissolution data [redacted]

Table 5.3.1: Bioequivalence Summary – **Iloperidone Tablets, 1 mg (Bio Batch)**

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT [redacted]% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID\Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 781984 Bio batch (Mfg date – July, 2013)	May 20, 2015	1 mg Tablet	12	Mean	86	89	91	95	96	97	Batch Analysis Section 3.2.P.5.4
				Range	[redacted]						
				%CV	6.38	4.17	3.76	3.13	2.85	2.66	
Reference Product – KKSZ (Exp date – October, 2015)	May 20, 2015	1 mg Tablet	12	Mean	97	101	101	100	101	100	
				Range	[redacted]						
				%CV	5.01	1.98	1.84	2.02	1.81	2.33	

Table 5.3.2: Bioequivalence Summary – **Iloperidone Tablets, 1 mg**

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID\Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782084 (Mfg date – December, 2013)	May 20, 2015	1 mg Tablet	12	Mean	84	88	90	95	97	98	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	10.20	8.36	6.85	4.11	3.02	2.47	
Reference Product – KKSZ (Exp date – October, 2015)	May 20, 2015	1 mg Tablet	12	Mean	97	101	101	100	101	100	
				Range	(b) (4)						
				%CV	5.01	1.98	1.84	2.02	1.81	2.33	

Table 5.3.3: Bioequivalence Summary – **Iloperidone Tablets, 2 mg**

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID\Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782085 (Mfg date – December, 2013)	May 20, 2015	2 mg Tablet	12	Mean	84	89	91	96	99	100	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	7.45	6.36	5.64	3.94	2.82	2.20	
Reference Product – KZDD (Exp date – October, 2015)	May 20, 2015	2 mg Tablet	12	Mean	97	99	99	100	100	100	
				Range	(b) (4)						
				%CV	3.11	1.43	1.21	0.85	0.76	0.79	

Table 5.3.4: Bioequivalence Summary – **Iloperidone Tablets, 4 mg**

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782086 (Mfg date – December, 2013)	May 20, 2015	4 mg Tablet	12	Mean	82	86	89	94	97	98	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	8.21	6.25	5.18	3.60	2.75	2.45	
Reference Product – KWDX (Exp date – January, 2016)	May 20, 2015	4 mg Tablet	12	Mean	73	83	87	96	99	100	
				Range	(b) (4)						
				%CV	12.21	9.55	7.58	3.26	1.43	1.49	

Table 5.3.5: Bioequivalence Summary – **Iloperidone Tablets, 6 mg**

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782087 (Mfg date – December, 2013)	May 20, 2015	6 mg Tablet	12	Mean	77	81	83	88	92	94	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	5.61	4.86	4.79	4.36	3.96	3.62	
Reference Product – KKTB (Exp date – September, 2015)	May 20, 2015	6 mg Tablet	12	Mean	74	87	93	98	99	100	
				Range	(b) (4)						
				%CV	10.91	6.50	4.03	1.88	1.46	1.32	

Table 5.3.6: Bioequivalence Summary – **Iloperidone Tablets, 8 mg**

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)(4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782088 (Mfg date – December, 2013)	May 20, 2015	8 mg Tablet	12	Mean	80	85	88	94	97	99	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	9.22	6.84	5.43	3.55	2.91	2.81	
Reference Product – KZDK (Exp date – October, 2015)	May 20, 2015	8 mg Tablet	12	Mean	81	86	90	95	98	99	
				Range	(b) (4)						
				%CV	11.23	8.17	6.32	4.16	3.21	2.73	

Table 5.3.7: Bioequivalence Summary – **Iloperidone Tablets, 10 mg**

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782089 (Mfg date – December, 2013)	May 20, 2015	10 mg Tablet	12	Mean	81	84	87	93	96	99	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	6.75	6.40	5.45	3.68	2.96	2.55	
Reference Product – MGSC (Exp date – November, 2015)	May 20, 2015	10 mg Tablet	12	Mean	77	83	87	94	97	98	
				Range	(b) (4)						
				%CV	12.13	8.47	5.68	3.23	2.94	2.80	

Table 5.3.8: Bioequivalence Summary – **Iloperidone Tablets, 12 mg**

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4) % (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782090 (Mfg date – December, 2013)	May 20, 2015	12 mg Tablet	12	Mean	81	83	85	90	92	94	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	6.57	6.08	5.11	3.63	3.47	3.74	
Reference Product – MDGD (Exp date – December, 2015)	May 20, 2015	12 mg Tablet	12	Mean	71	80	86	95	98	99	
				Range	(b) (4)						
				%CV	17.40	11.84	8.36	3.68	2.06	1.51	

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	207098
APPLICANT:	Taro Pharmaceutical U.S.A., Inc.
DRUG PRODUCT:	Iloperidone Tablets 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg

The Division of Bioequivalence III (DBIII) 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}

Hoainhon Nguyen Caramenico, M.S., M.S.
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

7. OUTCOME PAGE

ANDA: 207098

Reviewer: Chang, Yang **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
26162	5/29/2015	Other (REGULAR)	Study Amendment	1	1
26162	5/29/2015	Quality Assessment	Quality	5	5
				Total:	6

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	207098
Drug Product Name	Iloperidone Tablets
Strength (s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg
Applicant Name	Taro Pharmaceutical Industries Ltd.
Applicant Address	14 Hakitor Street, Haifa Bay, Israel, 2624761
US Agent Name and the mailing address	Taro Pharmaceuticals U.S.A. Inc. (Kavita Srivastava, Executive Director, Regulatory Affairs), 3 Skyline Drive, Hawthorne, NY 10532
US Agent's Telephone Number	914-345-9001 (b) (6)
US Agent's Fax Number	914-593-0078
Original Submission Date(s)	06/02/2014
Submission Date(s) of Amendment(s) Under Review	05/29/2015
Reviewer	Sam Chan
Dissolution Method	**ADEQUATE**
OVERALL REVIEW RESULT	**ADEQUATE**

I. EXECUTIVE SUMMARY

This is a review of the dissolution amendment.

There is no USP method but there is an FDA-recommended method for this product. In the original dissolution review[1], the firm's dissolution testing using the FDA-recommended method [500 mL of 0.1N HCl @ 37 ± 0.5°C, USP apparatus II at 50 rpm] (b) (4) In the DBII deficiency letter dated 04/27/2015, the firm was asked to provide dissolution data using the FDA-recommended.

In its current amendment dated May 29, 2015 the firm provided acceptable dissolution data using the FDA-recommended method (b) (4) The firm's proposed specification of NLT (b) (4)% (Q) in 30 minutes is also acceptable. The DB II acknowledges that the firm will follow the FDA-recommended method and its proposed specification.

As a result, the dissolution testing conducted is **adequate**.

[1] GDRP: ANDA 207098 under Biopharmaceutics Primary Review uploaded on 1/13/2015.

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)

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

II.3 USP Method (if any)

II.4 Summary of In Vitro Dissolution Data

The firm provided dissolution data for all strengths of test and reference using FDA-recommended method in its current amendment dated 5/29/2015.

Dissolution Data 1mg:

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID\Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 781984 Bio batch (Mfg date – July, 2013)	May 20, 2015	1 mg Tablet	12	Mean	86	89	91	95	96	97	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	6.38	4.17	3.76	3.13	2.85	2.66	
Reference Product – KKSZ (Exp date – October, 2015)	May 20, 2015	1 mg Tablet	12	Mean	97	101	101	100	101	100	
				Range	(b) (4)						
				%CV	5.01	1.98	1.84	2.02	1.81	2.33	

Dissolution Data 1 mg:

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID\Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782084 (Mfg date – December, 2013)	May 20, 2015	1 mg Tablet	12	Mean	84	88	90	95	97	98	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	10.20	8.36	6.85	4.11	3.02	2.47	
Reference Product – KKSZ (Exp date – October, 2015)	May 20, 2015	1 mg Tablet	12	Mean	97	101	101	100	101	100	
				Range	(b) (4)						
				%CV	5.01	1.98	1.84	2.02	1.81	2.33	

Dissolution Data 2 mg:

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)(4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID\Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782085 (Mfg date – December, 2013)	May 20, 2015	2 mg Tablet	12	Mean	84	89	91	96	99	100	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	7.45	6.36	5.64	3.94	2.82	2.20	
Reference Product – KZDD (Exp date – October, 2015)	May 20, 2015	2 mg Tablet	12	Mean	97	99	99	100	100	100	
				Range	(b) (4)						
				%CV	3.11	1.43	1.21	0.85	0.76	0.79	

Dissolution Data 4 mg:

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)(4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782086 (Mfg date – December, 2013)	May 20, 2015	4 mg Tablet	12	Mean	82	86	89	94	97	98	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	8.21	6.25	5.18	3.60	2.75	2.45	
Reference Product – KWDX (Exp date – January, 2016)	May 20, 2015	4 mg Tablet	12	Mean	73	83	87	96	99	100	
				Range	(b) (4)						
				%CV	12.21	9.55	7.58	3.26	1.43	1.49	

Dissolution Data 6 mg:

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782087 (Mfg date – December, 2013)	May 20, 2015	6 mg Tablet	12	Mean	77	81	83	88	92	94	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	5.61	4.86	4.79	4.36	3.96	3.62	
Reference Product – KKTB (Exp date – September, 2015)	May 20, 2015	6 mg Tablet	12	Mean	74	87	93	98	99	100	
				Range	(b) (4)						
				%CV	10.91	6.50	4.03	1.88	1.46	1.32	

Dissolution Data 8 mg:

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782088 (Mfg date – December, 2013)	May 20, 2015	8 mg Tablet	12	Mean	80	85	88	94	97	99	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	9.22	6.84	5.43	3.55	2.91	2.81	
Reference Product – KZDK (Exp date – October, 2015)	May 20, 2015	8 mg Tablet	12	Mean	81	86	90	95	98	99	
				Range	(b) (4)						
				%CV	11.23	8.17	6.32	4.16	3.21	2.73	

Dissolution Data 10 mg:

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782089 (Mfg date – December, 2013)	May 20, 2015	10 mg Tablet	12	Mean	81	84	87	93	96	99	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	6.75	6.40	5.45	3.68	2.96	2.55	
Reference Product – MGSC (Exp date – November, 2015)	May 20, 2015	10 mg Tablet	12	Mean	77	83	87	94	97	98	
				Range	(b) (4)						
				%CV	12.13	8.47	5.68	3.23	2.94	2.80	

Dissolution Data 12 mg:

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	500 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)(4)% (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Testing Date**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**						**Study Report Location**
					5	**10**	**15**	**30**	**45**	**60**	
Test Product – 782090 (Mfg date – December, 2013)	May 20, 2015	12 mg Tablet	12	Mean	81	83	85	90	92	94	Batch Analysis Section 3.2.P.5.4
				Range	(b) (4)						
				%CV	6.57	6.08	5.11	3.63	3.47	3.74	
Reference Product – MDGD (Exp date – December, 2015)	May 20, 2015	12 mg Tablet	12	Mean	71	80	86	95	98	99	
				Range	(b) (4)						
				%CV	17.40	11.84	8.36	3.68	2.06	1.51	

Dissolution Method SOP effective at the time of testing (Yes/No)	No (May 28. 2015)
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.	22 months for the bio-batch, 17 months for the rest.
Was the reference product expired at the time of dissolution testing (Yes/No)	No
Comments on the variability of the dissolution data	The variability of the data is adequate
For two-stage dissolution testing, comment on the method of medium change from acid stage to buffer stage.	N/A

III. REVIEW OF THE CURRENT SUBMISSION:

The firm's response to the three dissolution deficiencies and the reviewer's evaluation of this responses are provided in this section of the review.

Dissolution Deficiency #1:

Your dissolution testing is not acceptable. The Division of Bioequivalence does not encourage [redacted] (b) (4) in conducting dissolution testing. Please conduct dissolution testing on twelve (12) dosage units of unexpired batches of each test and reference product using the following FDA-recommended method:

USP Apparatus	II (paddle)
Rotation speed	50 rpm
Medium	0.1 N HCl
Volume	500 ml
Temperature	37.0 ± 0.5°C
Sampling Times	5, 10, 15, 30, 45 and 60 minutes

Firm's Response:

As per the Division of Bioequivalence request, Taro had conducted comparative dissolution testing of its lloperidone Tablets vs. the Reference Listed Drug (RLD) Fanapt® (Iloperidone) Tablets for all product strengths (1mg, 2mg, 4mg, 6mg, 8mg, 10mg, and 12mg). The dissolution testing was conducted according to the FDA-recommended dissolution method as detailed above, [redacted] (b) (4)

The comparative dissolution results show that Taro's Iloperidone Tablets is comparable to the reference product by means of dissolution with f2 values of >50%.

Based on these dissolution results, Taro acknowledges the Agency's recommendation to use the FDA recommended method (Apparatus II(paddle); 50rpm, 0.1N HCl, 500mL) [redacted] (b) (4) for testing dissolution at release and stability of its Iloperidone Tablets 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg. [redacted] (b) (4)

[redacted] (b) (4)

Therefore, based on the data generated, Taro is proposing acceptance criteria of NLT [redacted] (b) (4) % (Q) for the dissolution of its Iloperidone Tablets. The proposed specifications are enclosed in Module 3.2.P.5.1 and 3.2.P.8.1.

Reviewer's Comments:

- In its initial submission, the firm's dissolution testing data using the modified FDA-recommended method [500 mL of 0.1N HCl @ 37 ± 0.5°C, USP apparatus II at 50 rpm] (b) (4) for its test products Iloperidone Tablets, 1 mg (lot# 781984-bio-batch), 1 mg (lot# 782084), 2 mg (lot# 782085), 4 mg (lot# 782086), 6 mg (lot# 782087), 8 mg (lot# 782088), 10 mg (lot# 782089) and 20 mg (lot# 782090).

- In its current amendment dated 05/29/2015, the firm acknowledged the DBII recommended method [500 mL of 0.1N HCl @ 37 ± 0.5°C, USP apparatus II at 50 rpm]. The firm provided acceptable new dissolution data using the FDA-recommended and proposed specification of NLT (b) (4)% (Q) in 30 minutes. The DBII agrees the firm's proposed specification of NLT (b) (4)% in 30 minutes.

  Firm's response is satisfactory.

Dissolution Deficiency #2:

The Bioequivalence (BE) Summary Table 5 for 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths, for the dissolution data could not be located in the submission. Please submit Bioequivalence (BE) Summary Table 5, for the dissolution data of all the strengths.

Firm's Response:

The Bioequivalence (BE) Summary Table 5 for 1mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths, for the dissolution data is enclosed in Module 3.2.P.5.4. In addition the dissolution Table 5 was updated to include new dissolution data using FDA recommended method and provided in Module 2.7.1.

Reviewer's Comments:

The firm provided new dissolution summary data in Table 5 in Module 2.7.1. and individual tablet data in Module 3.2P.5.4

Firm's response is satisfactory.

Dissolution Deficiency #3:

The dissolution method was not in effect at the time of dissolution testing. You reported using the Analytical Method (Taro Research Institute (b) (4) effective date: May 19, 2014) for conducting dissolution testing. All the reported dissolution testing was conducted prior to the effective date: May 19, 2014. For future submissions, please submit dissolution data using an effective method.

Firm's Response:
Originally the batches were tested as per edition no. 04 of the dissolution method, which was effective at the time of exhibit batches release (December 2013). Later on, the dissolution method was updated to edition 05 (Effective May 19, 2014) to include a note regarding the stability of standard and sample solutions [redacted] (b) (4)

Future batches will be tested according to the current edition of method used at Taro at the time of testing.

Reviewer's Comments:

The initial concern regarding the effective date of the dissolution method is resolved.

The current SOP was not effective [redacted] (b) (4) when the new dissolution testing using the FDA-recommended method was done [redacted] (b) (4) Since there is only 8 days apart, and the current SOP [redacted] (b) (4) is the same as the previous [redacted] (b) (4) it is deemed acceptable . In future submissions, the firm should be informed that the dissolution SOP should be effective prior to the comparative dissolution testing.

IV. Deficiency Comment for Dissolution Testing

None.

V. Dissolution Recommendations

The in vitro dissolution testing conducted by Taro Pharmaceutical Industries Ltd. on its test product, Iloperidone Tablets, 1 mg (lot# 781984 – bio-batch), 1 mg (lot# 782084), 2 mg (lot# 782085), 4 mg (lot# 782086), 6 mg (lot# 782087), 8 mg (lot# 782088), 10 mg (lot# 782089) and 20 mg (lot# 782090), comparing it to [redacted] (b) (4) Fanapt® (iloperidone) tablets, 1 mg (lot# KKSZ), 2 mg (lot# KZDD), 4 mg (lot# KWDX), 6 mg (lot# KKTB), 8 mg (lot# KZDK), 10 mg (lot# MGSC) and 20 mg (lot# MDGD), respectively, is **adequate**.

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

ANDA: 207098

APPLICANT: Taro Pharmaceutical Industries Ltd.

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

The Division of Bioequivalence II (DBII) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Your dissolution testing using the FDA-recommended method is acceptable. Your proposed specification is also acceptable. We acknowledge that you will conduct the dissolution testing for your test product using the following FDA-recommended dissolution method and specification:

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

For future submissions, please be advised that the dissolution validation should be completed prior to the dissolution testing, and the dissolution method SOP should be effective at the time of testing.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the in vivo studies.

Sincerely yours,

{See appended electronic signature page}

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

VI. OUTCOME

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

DIVISION OF BIOEQUIVALENCE REVIEW

TEMPLATE 2 (SIMPLE IMMEDIATE RELEASE PRODUCTS)

ANDA No.	207098		
Drug Product Name	Iloperidone Tablets		
Strength(s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg		
Applicant Name	Taro Pharmaceutical U.S.A., Inc.		
Applicant Address	3 Skyline Drive Hawthorne, NY 10532		
Contact	Kavita Srivastava		
US agent's Telephone Number	914 345 9001 (b) (6)		
US Agent's Fax Number	914 593 0078		
US Agent's Email Address	Kavita.srivastava@taro.com		
Original Submission Date(s)	06/02/2014		
Submission Date(s) of Amendment(s) Under Review	N/A		
Reviewer	Yang Chang, Pharm.D., Ph.D.		
Study Number (s)	PKD_13_459	PKD_13_460	2013-3306
Study Type (s)	Pivotal Fasting	Pivotal Fed	Pilot Fasting
Strength (s)	1 mg	1 mg	1 mg
Clinical Site	Sun Pharmaceutical Industries Ltd		Pharma Medica Research Inc.
Clinical Site Address	Clinical Pharmacology Unit, Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (India)		4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6
Analytical Site	(b) (4)		
Analytical Site Address			
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete**	**Year 3 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**	
OVERALL REVIEW RESULT	**Inadequate**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
COMMUNICATION	☐ **ECD** ☒ **IR**		

	☐ NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
#1	**Fasting**	**1 mg**	**Adequate**
#1	**Fed**	**1 mg**	**Adequate**
#1	**Dissolution Waiver**	**2 mg**	**Inadequate**
#1	**Dissolution Waiver**	**4 mg**	**Inadequate**
#1	**Dissolution Waiver**	**6 mg**	**Inadequate**
#1	**Dissolution Waiver**	**8 mg**	**Inadequate**
#1	**Dissolution Waiver**	**10 mg**	**Inadequate**
#1	**Dissolution Waiver**	**12 mg**	**Inadequate**

- **EXECUTIVE SUMMARY**

This application contains the results of the fasting and fed bioequivalence (BE) studies comparing a test product, Taro Pharmaceutical U.S.A., Inc.'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 pivotal fasting and fed BE studies are adequate. The results are summarized in the tables below.

Iloperidone 1 mg Tablets Number of subject completed = 32 males, Dose: 1 mg Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals						
Fasted Bioequivalence Study (PKD_13_459)						
Parameter	**Test**	**N**	**Ref**	**N**	**Ratio %**	**90% C.I**
Iloperidone						
AUCo-t (pg.h/mL)	11557.68	32	11941.20	32	96.79	93.15 - 100.57
AUCo-∞ (pg.h/mL)	14965.66	32	14921.74	32	100.29	95.25 - 105.61
Cmax (pg /mL)	423.87	32	439.58	32	96.43	90.69 - 102.53
P88 Metabolite						
AUCo-t (pg.h/mL)	20347.85	31	21163.89	31	96.14	93.08 - 99.30
AUCo-∞ (pg.h/mL)	25988.12	31	27272.56	31	95.29	91.39 - 99.36
Cmax (pg /mL)	657.13	32	677.39	32	97.01	92.48 - 101.76

Iloperidone 1 mg Tablets Number of subject completed = 32 males, Dose: 1 mg Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals						
Fed Bioequivalence Study (PKD_13_460)						
Parameter	**Test**	**N**	**Ref**	**N**	**Ratio %**	**90% C.I**
Iloperidone						
AUCo-t (pg.h/mL)	13619.19	32	13707.53	32	99.36	94.92 - 104.00
AUCo-∞ (pg.h/mL)	17514.85	32	16859.04	32	103.89	98.25 - 109.86
Cmax (pg /mL)	470.34	32	478.87	32	98.22	92.87 - 103.88
P88 Metabolite						
AUCo-t (pg.h/mL)	27155.07	31	27580.41	31	98.46	95.33 - 101.69
AUCo-∞ (pg.h/mL)	34089.74	31	34198.39	31	99.68	95.58 - 103.96
Cmax (pg /mL)	742.74	31	777.65	31	95.51	91.85 - 99.32

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

The firm conducted a pilot fasting study using two investigational formulations of the Iloperidone Tablets, 1 mg (i.e., lot #781983 and lot #781984). The goal of the pilot study was to investigate the effect of the particle size distribution (PSD) of API on the BE. Both investigational formulations have identical composition but different PSD of API. The PK parameters of the pilot fasting study met the BE criteria for both formulations. The firm selected lot # 781984 for the pivotal studies.

The firm did not provide the intensity of the adverse events in the pilot study including the severity/intensity of the AEs (i.e., mild, moderate, severe, serious etc.). The firm will be asked to provide this information.

The dissolution testing data was reviewed separately.[1] The dissolution data are inadequate with respect to supporting waiver requests of the other strengths, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg.

The DB III denies the waivers of in vivo BE study requirements for the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths based on criteria set forth in 21 CFR § 320.22 (d) (2).

Based on evaluation of the submitted data, the OSIS inspection of the clinical and analytical sites for the current ANDA is not necessary. The studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The current ANDA reviewer determined that the findings of the OSIS inspection identified for other NDA are not expected to impact the BE study outcomes of the current ANDA. The OSIS inspection status for the current ANDA is considered complete at this time.

The application is inadequate.

[1] GDRP, ANDA-207098-ORIG-1, Biopharmaceutics Primary Review 207098D060214.doc Review Sam Chan 13-Jan-2015

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- **SUBMISSION SUMMARY**

1.1 Drug Product Information[2, 3]

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

*RLD

Fanapt® is a registered trademark of Vanda Pharmaceuticals Inc. and is used by Novartis Pharmaceuticals Corporation under license.[3] The Fanapt® is manufactured (b) (4)

1.2 PK/PD Information

Bioavailability	The relative bioavailability of the tablet formulation compared to oral solution is 96%.
Food Effect	Administration of iloperidone with a standard high-fat meal did not significantly affect the 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	2 to 4 hours
Metabolism	Iloperidone is metabolized primarily by three biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and O-demethylation (mediated by CYP3A4). There are two predominant iloperidone metabolites, P95 and P88. The iloperidone metabolite P95 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively. Iloperidone and P88 are not substrates of P-gp and iloperidone is a weak P-gp inhibitor.
Excretion	Elimination of iloperidone is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. The bulk of the radioactive materials were recovered in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with feces accounting for 19.9% (EM) to 22.1% (PM) of the dosed radioactivity.

[2] http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=022192&TABLE1=OB_Rx
[3] RLD label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022192s013lbl.pdf
[4] EDR, NDA 022192, 09/27/2007, module 3.2.P.3.1

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.
Dosage and Administration	FANAPT 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 FANAPT tablets is 1 mg twice daily. Dose increases to reach the target range of 6-12 mg twice daily (12_24 mg/day) may be made with daily dosage adjustments not to exceed 2 mg twice daily (4 mg/day). The maximum recommended dose is 12 mg twice daily (24 mg/day). FANAPT doses above 24 mg/day have not been systematically evaluated in the clinical trials. Efficacy was demonstrated with FANAPT 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 FANAPT. 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 FANAPT use are dose related. FANAPT can be administered without regard to meals.
Maximum Daily Dose	24 mg

1.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-way crossover *in-vivo*
	Strength:	1 mg (dose=1 mg*2 or 1 mg*3 depending on the assay sensitivity)
	Subjects:	Healthy males and non-pregnant females, general population
	Additional Comments:	N/A

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

Analytes to measure (in plasma/serum/blood):	Iloperidone and the active P88 metabolite in plasma
Bioequivalence based on:	90% CI of iloperidone

Waiver request of in-vivo testing:	2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg, based on (i) acceptable bioequivalence study using the 1 mg tablets, (ii) proportional similarity in the formulations of the 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg strengths and (iii) acceptable comparable in vitro dissolution testing on all strengths.	
Source of most recent recommendations or provide the link to the current draft guidance:	http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234968.pdf	
Summary of OGD or DB History	Pending ANDAs (Not Yet Reviewed)	Yes
	Approved ANDAs	No
	Previously Reviewed ANDAs	Yes
	Protocols	No
	Controls	No

1.4 Pre-Study Bioanalytical Method Validation

Study # 2013-3306 (pilot fasted)

Information Requested	**Data**
Bioanalytical method validation report location	N/A
Analyte	**Iloperidone**
Internal standard (IS)	Iloperidone-^{13}C-d_3
Method description	liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method
Limit of quantitation	5.00 pg/mL
Average recovery of drug (%)	73.0 % to 80.0 %
Average recovery of IS (%)	77.1 %
Standard curve concentrations (units/mL)	5.00, 10.0, 25.0, 60.0, 150, 350, 800 and 1250 pg/mL
QC concentrations (units/mL)	QC A: 15.0 pg/mL, QC B: 625 pg/mL, QC C: 1000 pg/mL
QC Intraday precision range (%)	0.6 % to 5.5 %
QC Intraday accuracy range (%)	99.0 % to 106.3 %
QC Interday precision range (%)	2.7 % 3.1 %
QC Interday accuracy range (%)	102.0 % to 102.6 %
Bench-top stability (hrs)	19.50 hours @ room temperature
Stock stability (days)	28 days@ 5 ± 3°C
Processed stability (hrs)	49.50 hours @ approximately 5°C
Freeze-thaw stability (cycles)	4 cycles @ -25 ± 10°C
Long-term storage stability (days)	28 days @ -25 ± 10°C
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	No interfering peaks noted in blank plasma samples
Analyte	**P88 Metabolite**
Internal standard (IS)	Iloperidone-13C-d3 Metabolite P88
Method description	liquid chromatographic (LC) tandem mass spectrometric

	detection (MS/MS) method
Limit of quantitation	5.00 pg/mL
Average recovery of drug (%)	73.6 % to 78.7 %
Average recovery of IS (%)	78.1 %
Standard curve concentrations (units/mL)	5.00, 10.0, 25.0, 60.0, 150, 350, 800 and 1250 pg/mL
QC concentrations (units/mL)	QC A: 15.0 pg/mL, QC B: 625 pg/mL, QC C: 1000 pg/mL
QC Intraday precision range (%)	1.0 % to 3.2 %
QC Intraday accuracy range (%)	98.1 % to 105.3 %
QC Interday precision range (%)	1.9 % 2.4 %
QC Interday accuracy range (%)	100.6 % to 102.0 %
Bench-top stability (hrs)	19.50 hours @ room temperature
Stock stability (days)	28 days@ 5 ± 3°C
Processed stability (hrs)	49.50 hours @ approximately 5°C
Freeze-thaw stability (cycles)	4 cycles @ -25 ± 10°C
Long-term storage stability (days)	28 days @ -25 ± 10°C
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	No interfering peaks noted in blank plasma samples

Studies # PKD 13 459 & PKD 13 460 (pivotal fasted & fed)

Information Requested	**Data**
Bioanalytical Method Validation Report location	Report No.: [redacted] (b) (4) Section 5-3-1-4 (Method Validation Report) ; Page – 1 - 164
Analyte	**Iloperidone**
Internal Standard (IS)	D3 Iloperidone
Method Description	Extraction Technique: Solid Phase Extraction; Detection mode: Tandem Mass Spectrometry with positive mode
Limit of quantitation	LLOQ : 20.5pg/mL / 21.5pg/mL(*)
Average recovery of drug (%)*	80.3% to 95.4%
Average recovery of IS (%)*	82.3%
Standard curve concentrations (pg/mL)	20.5, 40.9, 186.7, 433.6, 1108.0, 1589.7, 1926.9, 2505.0
QC Concentrations (pg/mL)	60.3, 180.8, 626.9, 1205.6, 2049.5
QC Intraday precision range (%)	2.1 % to 7.9%
QC Intraday accuracy range (%)	96.8% to 101.7%
QC Inter day precision range (%)	1.0% to 11.0%
QC Inter day accuracy range (%)	82.7% to 109.5%
Bench-top stability (hrs)	9 hours at room temperature
Stock stability (days)	14 days @ 2-8°C
Processed stability (hrs)	68 hours @ 6°C
Freeze-thaw stability (cycles)	03 cycles at -20±5°C, -35±5°C & -65±10°C
Long term storage stability (Days)	53 days at -20±5°C, -35±5°C & -65±10°C
Dilution Integrity	Concentration diluted 5-fold
Selectivity	No Significant Interference observed in blank plasma samples
Analyte	**P88 Metabolite**
Internal Standard (IS)	D3 Iloperidone
Method Description	Extraction Technique: Solid Phase Extraction; Detection mode: Tandem Mass Spectrometry with positive mode

Limit of quantitation	14.9 pg/mL
Average recovery of drug (%)*	66.2% to 76.6%
Average recovery of IS (%)*	82.3%
Standard curve concentrations (pg/mL)	14.9, 29.8, 148.8, 347.3, 868.2, 1265.1, 1562.7, 2009.2
QC Concentrations (pg/mL)	44.1, 132.3, 500.6, 953.5, 1621.0
QC Intraday precision range (%)	2.0% to 4.5%
QC Intraday accuracy range (%)	95.5% to 105.4%
QC Inter day precision range (%)	0.7% to 7.7%
QC Inter day accuracy range (%)	85.5% to 111.5%
Bench-top stability (hrs)	9 hours at room temperature (in Plasma)
Stock stability (days)	14 days @ 2-8°C
Processed stability (hrs)	68 hours @ 6°C
Freeze-thaw stability (cycles)	03 cycles at -20±5°C, -35±5°C & -65±10°C
Long term storage stability (Days)	53 days at -20±5°C, -35±5°C & -65±10°C
Dilution Integrity	Concentration diluted 5-fold
Selectivity	No Significant Interference observed in blank plasma samples

* Relative recovery

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

Comments on the Pre-Study Method Validation:

- The same anticoagulant K2EDTA was used in the pre-method validation and sample analysis.
- The long-term storage stability is adequate to cover the study period.
- The pre-study method validation is adequate.

1.5 In Vivo Studies

Study # PKD_13_459 (pivotal fasted)

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)						Study Report Location
					Cmax** (pg/mL)	Tmax* (h)	AUC0-t** (pg.h/mL)	AUC∞ (pg.h/mL)**	T½ (h)**	Kel (hr-1)**	
					Iloperidone						
PKD_13_459	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Iloperidone 1 mg Tablets of Taro Pharmaceutical Industries ltd., and Fanapt® (Iloperidone) 1 mg Tablets off (b) (4) under Fasting Conditions	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study under fasting conditions	**Test** Dose: 1 mg Iloperidone 1 mg Tablets, Batch No.: 781984 (Taro Pharmaceuticals USA Inc., USA) p.o.	32 healthy subjects (32 M/ 0 F) 29.3 years (19-43)	**Test** 482.78 (49.7)	2.834 (1.67 - 6.00)	12623.33 (41.7)	16125.997 (39.7)	58.35 (35.3)	0.0131 (29.4)	5.3.1.2
					Ref. 499.32 (46.9)	2.667 (2.00 - 5.00)	13114.70 (41.7)	16173.005 (39.2)	51.54 (22.1)	0.0141 (22.2)	
			Ref. Dose: 1 mg Fanapt® 1 mg Tablets, Lot No.: GVSB (b) (4) p.o.		**P88 Metabolite**						
					Test 712.21 (45.8)	3.75 (2.00 - 6.00)	21385.73 (41.1)	27515.017 (47.0)	57.87 (28.7)	0.0128 (25.2)	
					Ref. 727.43 (40.2)	3.50 (2.00 - 4.50)	22059.58 (40.4)	28504.766 (41.1)	60.67 (22.3)	0.0119 (19.6)	

** Presented as arithmetic mean (CV%)
* Presented as median and range

Study # PKD_13_460 (pivotal fed)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route)	Subjects (No. (M/F) Type	Mean Parameters (+/-SD)						Study Report Location
					Cmax** (pg/mL)	Tmax* (h)	AUC0-t** (pg.h/mL)	AUC∞ (pg.h/mL)*	T½ (h)**	Kel (hr-1)**	

			[Product ID]	Age: mean (Range)				*			
PKD_13_460	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Iloperidone 1 mg Tablets of Taro Pharmaceutical Industries ltd., and Fanapt® (Iloperidone) 1 mg Tablets off (b) (4) under Fed Conditions	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study under fed conditions.	**Test** Dose: 1 mg Iloperidone 1 mg Tablets, Batch No.: 781984 (Taro Pharmaceuticals USA Inc., USA) p.o. **Ref.** Dose: 1 mg Fanapt® 1 mg Tablets, Lot No.: GVSB (b) (4) p.o.	32 healthy subjects (32 M/ 0 F) 31.3 years (21-43)	**Iloperidone**						5.3.1.2
					Test 520.11 (42.9)	4.00 (1.50 - 6.00)	14832.29 (42.3)	19115.587 (42.0)	61.68 (59.8)	0.0134 (36.9)	
					Ref. 535.73 (46.8)	3.83 (2.00 - 6.00)	15062.63 (44.7)	18603.485 (45.7)	51.19 (27.1)	0.0145 (25.4)	
					P88 Metabolite						
					Test 753.22 (23.7)	5.50 (2.67 - 8.00)	28134.73 (26.7)	35689.190 (29.8)	56.72 (19.3)	0.0126 (16.1)	
					Ref. 788.30 (26.1)	5.50 (3.33 - 8.00)	28574.01 (28.5)	35887.168 (31.3)	54.99 (18.9)	0.0131 (19.0)	

** Presented as arithmetic mean (CV%)
* Presented as median and range

Study #2013-3306 (pilot fasted)

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)						Study Report Location
					Cmax** (pg/mL)	Tmax* (h)	AUC0-t** (pg.h/mL)	AUC∞ (pg h/mL)**	T½ (h)**	Kel (hr-1)**	
2013-3306	A Pilot Single-Dose, Comparative Bioavailability	Open-label, single-dose, randomized, 3-period, 3-	**Test A** Dose: 1 mg Iloperidone 1 mg Tablets, Batch No.:	15 healthy subjects (7 M/ 8 F)	**Analyte: Iloperidone**						2.7 OGD tables
					Test A 853.07 (41)	2.50 (1.67-6.00)	11347.36 (31)	16264.88 (39)	45.81 (25)	0.0159 (23)	

	Study of Three Formulations of Iloperidone 1 mg Tablets under Fasting Conditions	treatment, 3-sequence, crossover	781983 (Taro Pharmaceuticals USA Inc., USA) p.o.	41 years (24-57)	**Test B** 835.00 (36)	2.50 (1.67-5.00)	11356.06 (28)	15950.11 (31)	44.09 (21)	0.0164 (22)	
			Test B Dose: 1 mg Iloperidone 1 mg Tablets, Batch No.: 781984 (Taro Pharmaceuticals USA Inc., USA) p.o.		**Ref.C** 829.67 (35)	2.00 (1.33-4.50)	10819.52 (23)	15965.88 (31)	48.13 (34)	0.0157 (27)	
					Analyte: P88 Metabolite						
					Test A 528.80 (46)	4.00 (2.50-10.00)	16646.11 (48)	22735.65 (56)	35.80 (18)	0.0199 (17)	
			Ref. Dose: 1 mg Fanapt® 1 mg Tablets, Lot No.: GVSB (b) (4) p.o.		**Test B** 543.47 (42)	4.50 (2.50-8.00)	17092.42 (44)	23877.38 (47)	39.77 (19)	0.0180 (18)	
					Ref. 500.80 (38)	4.50 (2.50-10.00)	16243.32 (37)	23196.44 (45)	40.90 (22)	0.0176 (17)	

** Presented as arithmetic mean (CV%)

* Presented as median and range

Table 2. Reanalysis of Study Samples

Study# PKD_13_459 (pivotal fasted)

Study Number: PKD_13_459 Location in final report: Section 5-3-1-4; Pages 32, 33								
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
Analyte	**Iloperidone**							
Pharmacokinetics[1]	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	1	0	0.06	0.00	1	0	0.06	0.00
Incomplete analysis	1	0	0.06	0.00	1	0	0.06	0.00
Concentration/ Response in pre-dose samples	1	1	0.06	0.06	0	0	0.00	0.00
Total	**3**	**1**	**0.19**	**0.06**	**2**	**0**	**0.13**	**0.00**
Analyte	**P88 Metabolite**							
Pharmacokinetics[1]	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	1	0	0.06	0.00	1	0	0.06	0.00
Incomplete analysis	1	0	0.06	0.00	1	0	0.06	0.00
Concentration/ Response in pre-dose samples	9	8	0.56	0.50	1	2	0.06	0.13
Total	**11**	**8**	**0.69**	**0.50**	**3**	**2**	**0.19**	**0.13**

[1] - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Study# PKD_13_460 (pivotal fed)

Study Number: PKD_13_460 Location in final report: Section 5-3-1-4; Pages 31, 32								
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
Analyte	**Iloperidone**							
Pharmacokinetics[1]	0	0	0.00	0.00	0	0	0.00	0.00

Unacceptable internal standard response	1	3	0.06	0.19	1	3	0.06	0.19
Concentration/ Response in pre-dose samples	1	3	0.06	0.19	0	1	0.00	0.06
Total	**2**	**6**	**0.13**	**0.38**	**1**	**4**	**0.06**	**0.25**
Analyte	**P88 Metabolite**							
Pharmacokinetics[1]	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	1	3	0.06	0.19	1	3	0.06	0.19
Concentration/ Response in pre-dose samples	9	11	0.56	0.69	1	1	0.06	0.06
Total	**10**	**14**	**0.63**	**0.88**	**2**	**4**	**0.13**	**0.25**

[1] - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Study # 2013-3306 (pilot fasted)

Study No. 2013-3306 Additional information, 14.0 Analytical Report, Page(s): N/A												
Reason why assay was repeated	**Number of samples reanalyzed**						**Number of recalculated values used after reanalysis**					
	Actual number			**% of assays**			**Actual number**			**% of assays**		
	Test A	**Test B**	**Ref.**	**Test A**	**Test B**	**Ref.**	**Test A**	**Test B**	**Ref.**	**Test A**	**Test B**	**Ref.**
Analyte	**Iloperidone**											
Pharmacokinetic[1]	0	0	0	0	0	0	0	0	0	0	0	0
AULOQ[2]	5	5	2	1.52	1.52	0.61	5	5	2	1.52	1.52	0.61
UISR[3]	0	1	3	0	0.30	0.91	0	1	3	0	0.30	0.91
Total	**5**	**6**	**5**	**1.52**	**1.82**	**1.52**	**5**	**6**	**5**	**1.52**	**1.82**	**1.52**
Analyte	**P88 Metabolite**											
Pharmacokinetic[1]	0	0	0	0	0	0	0	0	0	0	0	0
UISR[3]	0	1	2	0	0.30	0.61	0	1	2	0	0.30	0.61
Total	**0**	**1**	**2**	**0**	**0.30**	**0.61**	**0**	**1**	**2**	**0**	**0.30**	**0.61**

[1] - If no repeats were performed for pharmacokinetic reasons, insert "0.0."
[2] - Above the Upper Limit of Quantitation;
[3] - Unacceptable Internal Standard Response.

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

Study # 2013-3306 (pilot fasted)

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Repeat Sample Analysis Procedure And Acceptance Criteria

Studies # PKD 13 459 & PKD 13 460 (pivotal fasted & fed)

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Repeat sample(s) identification, re-analysis and reporting of final concentration (Revision No.: 06)

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

Comments from the Reviewer:

- The reviewer only reviewed the data of the parent drug iloperidone in the current review for acceptability for the pivotal fasting and fed studies. The metabolite data of the active P88 metabolite are considered as supportive information and were not reviewed in detail.
- There was no pharmacokinetic repeat in the pivotal fasting and fed studies.
- There were one repeat under code B (unacceptable internal standard response), one repeat under code C (incomplete analysis), and 2 repeats under code H (Concentration/ Response in pre-dose samples) in pivotal fasting study. The firm provided raw data to support these repeats. These samples were repeated according to pre-established SOP.
- There were 4 repeats under code B (unacceptable internal standard response) and 4 repeats under code H (Concentration/ Response in pre-dose samples) in the pivotal fed study. The firm provided raw data to support these repeats. These samples were repeated according to pre-established SOP.

1.6 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested, if applicable	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Waiver regulation cited?	21 CFR 320.22 (d) (2)
Strengths considered for 21 CFR 320.24 (b)(6)	No
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	**WAIVERS DENIED**
If not then why?	The firm's dissolution data is not acceptable.

1.7 Deficiency Comments

Please see deficiency letter.

1.8 Comments for Other OGD Disciplines

Discipline	Comment
--	

- **APPENDIX**

1.9 Individual Study Reviews

1.9.1 Single-dose Fasting Bioequivalence Study

1.9.1.1 Study Design

Table 4. Study Information

Study Number	PKD_13_459
Study Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of iloperidone 1 mg tablets of taro pharmaceutical industries ltd., and fanapt® (iloperidone) 1 mg tablets of novartis pharmaceuticals corporation, in 32 healthy human adult subjects under fasting conditions
Clinical Site (Name & Address)	Clinical Pharmacology Unit, Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (India) Phone Number: 91-265-2350789, 91-265-6615500 Fax: 91-265-2354897
Principal Investigator	Dr. Aman Khanna MD Aman.Khanna@sunpharma.com
Dosing Dates	Period I: 05 December 2013, Period II: 19 December 2013
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	From 03rd January, 2014 to 21st January, 2014 for Iloperidone and P88 Metabolite
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	48 days, -20^{0}C$\pm$5^{0}C to -65^{0}C$\pm$10^{0}C

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Iloperidone 1 mg Tablets	Fanapt® 1 mg Tablets
Manufacturer	Taro Pharmaceutical Industries Ltd., Israel	Vanda Pharms Inc
Batch/Lot No.	781984	GVSB

Manufacture Date	07/2013	N/A
Expiration Date	N/A	04/2013
Strength	1 mg	1 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	100.6%	100.5%
Content Uniformity (expressed as mean, %CV or per USP)	(b) (4) Meets current USP <905> requirements (Acceptance value L1<15.0)	N/A
Dose Administered	1 x 1 mg	1 x 1 mg
Route of Administration	Oral	Oral

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	Yes

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

Number of Subjects	**Enrolled: 34** **Dosed: 32** **Completed: 32** **Samples Analyzed: 1594** **Data Analyzed: 32**
No. of Sequences	2
No. of Periods	2
No. of Treatment	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme (Sequence of T and R)	**Yes (module 5.3.1.2)**
Blood Sampling Times	Total 25 blood samples in each period were drawn into vacutainers containing K_2EDTA as an anticoagulant, prior to drug administration pre-dose (10 mL each) and at 0.333, 0.667, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.500, 4.000, 4.500, 5.000, 6.000, 8.000, 10.000, 12.000, 16.000, 24.000, 36.000, 48.000, 72.000, 96.000 and 120.000 hours post dosing (1 x 5 mL each) in each study period. The pre-dose and post-dose samples were collected by direct vein puncture.

Blood Sample Processing & Storage (include storage temperature)	All the study blood samples were centrifuged at 3300 rpm under refrigeration at 4 ± 2°C for 15 min within 1.5 hr of blood sampling collection. The resulting plasma samples from each blood samples were divided in to two aliquots (original & duplicate) and stored within 2 hours after collection in suitably labeled polypropylene tubes at ≤ -15°C until transfer of study sample. The frozen plasma aliquots, accompanied by an inventory list and sufficient dry ice to maintain the aliquots in a frozen state were sent to the analytical facility in shipments through internal courier on 02 January 2014. The plasma samples of period I were stored at clinical facility at ≤ -15°C for 29 days (05 December 2013 to 02 January 2014). The plasma samples of period II were stored at clinical facility at ≤ -15°C for 15 days (19 December 2013 to 02 January 2014).

Comments on Study Design:

The study design is acceptable.

1.9.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study Number PKD 13 459			
		Treatment Groups	
		Test Product N = 32	Reference Product N = 32
Age (Years)	Mean ± SD Range	29.3 +/- 6.75 19 – 43	29.3 +/- 6.75 19 – 43
Age Groups	< 18 18-40 41-64 65-75 >75	0 (0.0%) 30 (93.8 %) 2 (6.3%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 30 (93.8 %) 2 (6.3%) 0 (0.0%) 0 (0.0%)
Sex	Male Female	32 (100.0%) 0 (0.0%)	32 (100.0%) 0 (0.0%)
Race	Asian Black Caucasian Hispanic Other	32 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	32 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
BMI	Mean ± SD Range	21.52 ± 2.325 18.6 – 24.9	21.52 ± 2.325 18.6 – 24.9
Other Factors		N/A	N/A

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
--			

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Number: PKD_13_459	
MedDRA System Organ Class Preferred Term	Test	Reference
Investigations[1]		
Aspartate aminotransferase increased	2 (66.7)	
Alanine aminotransferase increased	1 (33.3)	
Total	**3 (100.0)**	

[1] Since no biochemistry assessment (AST, ALT) was done after screening until check-out of period II, these adverse events were considered to be emerged from both the formulations.

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
--				

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

- There is no substantial difference between the test and reference product for adverse event profile.
- Two subjects experienced 3 post dose adverse events in this study. Given no biochemistry assessment (AST, ALT) was done after screening until check-out of period II, these adverse events were considered to be possibly related to both the formulations.

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

No deaths and serious adverse events were reported during the study.

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

No.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
--		

Comments:

No dropout and protocol deviation were reported in the fasting study.

1.9.1.3 Bioanalytical Results

Table 11. Sample Analysis Calibration and Quality Control

Study# PKD_13_459 (pivotal fasted) - Iloperdone

Bioequivalence Study Number: PKD_13_459										
Analyte	**Iloperidone**									
Parameter	**Standard Curve Samples**									
Concentration (pg/mL)	21.2	21.2	42.3	193.1	448.4	1145.9	1644.1	1992.8	2491.0	2491.0
Inter Day Precision (% CV)	4.2	4.2	3.5	2.1	2.4	1.9	2.5	1.6	1.5	2.2
Inter Day Accuracy (% Actual)	100.7	99.9	98.1	104.3	99.8	98.7	100.5	99.8	99.2	99.0
Linearity	0.9930 to 0.9998									
Linearity range (pg/mL)	21.2 to 2491.0									
Limit of Quantitation (pg/mL)	21.2									

Study# PKD_13_459 (pivotal fasted) - Iloperdone

Bioequivalence Study Number: PKD_13_459					
Analyte	**Iloperidone**				
Parameter	**Quality Control Samples**				
Concentration (pg/mL)	62.5	187.6	650.3	1225.5	2050.8
Inter Day Precision (% CV)	3.2	2.9	2.1	2.5	1.8
Inter Day Accuracy (% Actual)	101.0	102.8	99.1	98.7	99.1

Study# PKD_13_459 (pivotal fasted) - P88 Metabolite

Bioequivalence Study Number: PKD_13_459										
Analyte	**P88 Metabolite**									
Parameter	**Standard Curve Samples**									
Concentration (pg/mL)	15.4	15.4	30.8	147.7	344.7	861.7	1255.7	1551.1	1994.3	1994.3
Inter Day Precision (% CV)	4.6	4.6	3.7	2.6	3.1	3.0	3.0	2.5	1.8	2.7
Inter Day Accuracy (% Actual)	101.1	100.7	95.8	103.0	100.4	98.6	101.2	100.1	99.7	99.5
Linearity	0.9967 to 0.9998									
Linearity range (pg/mL)	15.4 to 1994.3									

Limit of Quantitation (pg/mL)	15.4

Study# PKD 13 459 (pivotal fasted) - P88 Metabolite

Bioequivalence Study Number: PKD_13_459					
Analyte	**P88 Metabolite**				
Parameter	**Quality Control Samples**				
Concentration (pg/mL)	45.9	137.8	521.4	993.1	1638.7
Inter Day Precision (% CV)	4.9	3.3	2.9	2.7	2.7
Inter Day Accuracy (% Actual)	100.0	100.2	96.4	98.9	99.6

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

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

Table 12. SOP's Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Estimation of Iloperidone and its P88 Metabolite in human K2EDTA plasma using Ultra High Performance Liquid Chromatography Method with Tandem mass spectrometry-(b) (4)
		Evaluation of stability of drug(s) in biological matrix and solutions.
		Bioanalytical Method Validation
		Verification of Chromatograms , Peak Integration and Chromatographic Acceptance Criteria
		Repeat sample(s) identification, re-analysis and reporting of final concentration
		Procedure for detection of statistical outliers
		Chromatographic Analysis of Study Sample
		Preparation, identification and acceptance criteria of stock solutions, calibration standards, quality control samples.
		Identification and reanalysis of incurred samples
		Partial Bioanalytical Method Validation

Comments:

- The calibration was produced from eight nominal concentration plasma samples over the linear ranges of 21.2pg/mL to 2491.0pg/mL for Iloperidone and 15.4pg/mL to 1994.3pg/mL for P88 Metabolite. The firm used duplicated samples for lowest and highest calibration standards, according SOP [redacted] (b) (4)
- The calibration and quality control data for the sample analysis are acceptable.
- The firm conducted the Incurred Sample Reanalysis (ISR) in accordance with the SOP, and demonstrated that 97.5% (156 out of 160) of samples for iloperidone were within the acceptance range of ± 20 % for the percent difference between the original and reanalyzed values.

1.9.1.4 Pharmacokinetic Results

Is there a Tmax difference between T and R	No
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Yes

Overall Comment:

The fasting study is adequate.

Table 13. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Firm-Submitted Data in Firm's Format)

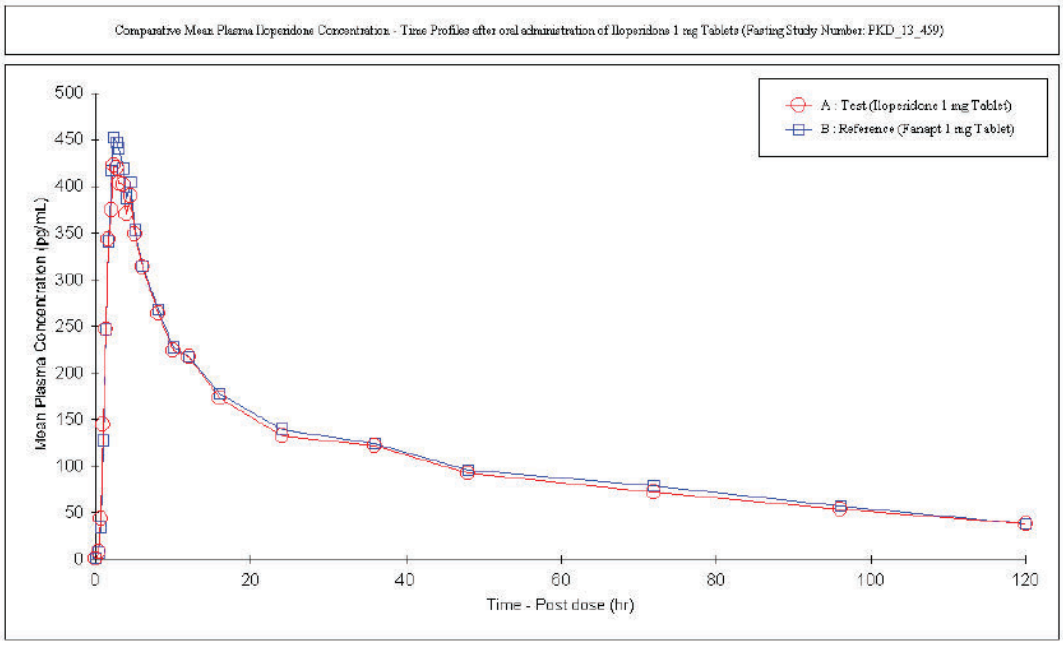
Least Square Means (pg/mL)

Collection Time (hr.)	TestLSM	RefLSM	# Significance	p Value
0.000	0.0000	0.6656	None	0.3253
0.333	7.7656	6.7937	None	0.7315
0.667	43.3781	33.7625	None	0.1178
1.000	144.0438	126.8781	None	0.4136
1.333	245.8094	246.8156	None	0.9642
1.667	343.2656	340.3875	None	0.9039
2.000	374.6750	416.4594	None	0.0661
2.333	422.7031	452.2250	None	0.3100
2.667	419.9937	447.7437	None	0.1609
3.000	402.9000	440.8281	None	0.0827
3.500	402.2031	418.6156	None	0.3855
4.000	370.5531	387.0938	None	0.3370
4.500	389.2656	403.6156	None	0.3082
5.000	348.2312	353.0219	None	0.6402
6.000	313.8031	316.0174	None	0.8537
8.000	263.0094	267.6250	None	0.5509
10.000	223.1406	227.4500	None	0.5559
12.000	217.2719	217.0656	None	0.9760
16.000	172.3594	176.9875	None	0.4684
24.000	131.9563	139.0438	None	0.1410
36.000	121.0125	123.6469	None	0.5614
48.000	92.1687	95.5219	None	0.2178
72.000	71.4351	78.6222	None	0.0523
96.000	52.9657	56.2049	None	0.0715
120.000	37.4875	37.0658	None	0.8423

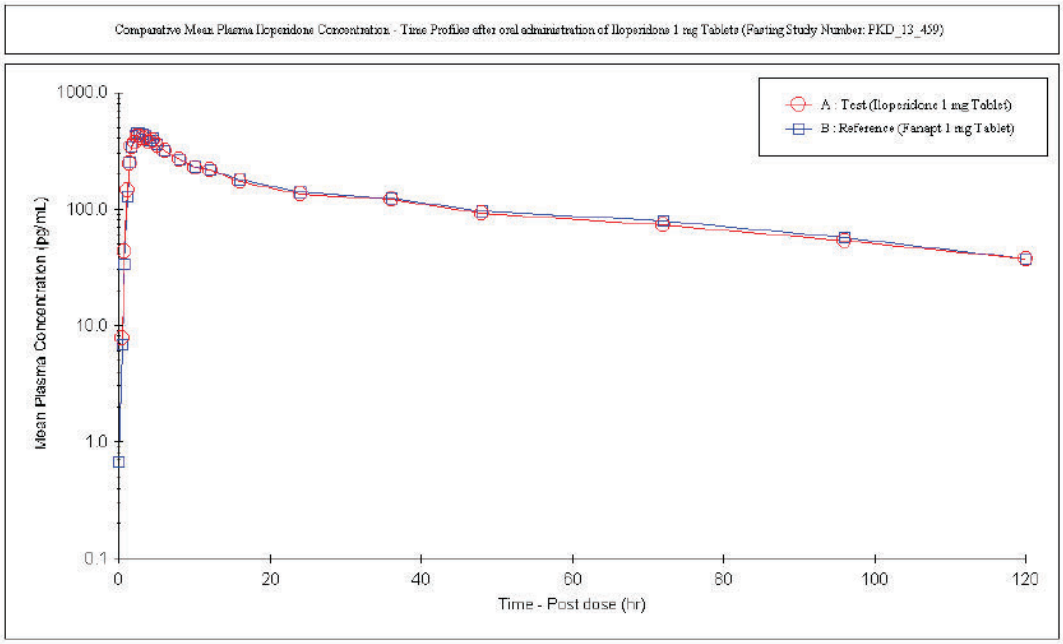
Results of the statistical evaluation by ANOVA (α =0.05) for the hypothesis of equal treatment effects. None indicate that no statistical significant difference was detected between treatment means (P >0.05) at the sampling time evaluated.

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

Linear Plot of Mean Plasma Concentration-Time profile of Iloperidone (N = 32):



Semi Logarithmic Plot of Mean Plasma Concentration-Time profile of Iloperidone (N=32):



1.9.2 Single-dose Fed Bioequivalence Study

1.9.2.1 Study Design

Table 14. Study Information

Study Number	PKD_13_460
Study Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of iloperidone 1 mg tablets of taro pharmaceutical industries ltd., and fanapt® (iloperidone) 1 mg tablets of novartis pharmaceuticals corporation, in 32 healthy human adult subjects under fed conditions.
Clinical Site (Name & Address)	Clinical Pharmacology Unit, Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (India) Phone Number: 91-265-2350789, 91-265-6615500 Fax: 91-265-2354897
Principal Investigator	Dr. Aman Khanna MD Aman.Khanna@sunpharma.com
Dosing Dates	Period I: 05 December 2013, Period II: 19 December 2013
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	From 04th January, 2014 to 21st January, 2014 for Iloperidone and P88 Metabolite
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	48 days, $-20^0C \pm 5^0C$ to $-65^0C \pm 10^0C$

Table 15. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Iloperidone 1 mg Tablets	Fanapt® 1 mg Tablets
Manufacturer	Taro Pharmaceutical Industries Ltd., Israel	(b) (4)
Batch/Lot No.	781984	GVSB
Manufacture Date	07/2013	N/A
Expiration Date	N/A	04/2013
Strength	1 mg	1 mg

Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	100.6%	100.5%
Content Uniformity (expressed as mean, %CV or per USP)	(b) (4) Meets current USP <905> requirements (Acceptance value L1<15.0)	N/A
Dose Administered	1 x 1 mg	1 x 1 mg
Route of Administration	Oral	Oral

Was the drug product administered per labeling?	Yes

Table 16. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled: 33** **Dosed: 32** **Completed:32** **Samples Analyzed:1597** **Data Analyzed: 32**
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme (Sequence of T and R)	**Yes (module 5.3.1.2)**
Blood Sampling Times	Total 25 blood samples in each period were drawn into vacutainers containing K_2EDTA as an anticoagulant, prior to drug administration pre-dose (10 mL each) collected within 1 hour prior to schedule dosing, and at 0.500, 1.000, 1.500, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 5.500, 6.000, 7.000, 8.000, 12.000, 16.000, 24.000, 36.000, 48.000, 72.000, 96.000 and 120.00 hours post dosing (1 x 5 mL each) in each study period. The predose and post-dose samples were collected by direct vein puncture.

Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	All the study blood samples were centrifuged at 3300 rpm under refrigeration at 4 ± 2°C for 15 min within 1.5 hr of blood sampling collection. The resulting plasma samples from each blood samples were divided in to two aliquots (original & duplicate) and stored within 2 hours after collection in suitably labeled polypropylene tubes at ≤ -15°C until transfer of study sample. The frozen plasma aliquots, accompanied by an inventory list and sufficient dry ice to maintain the aliquots in a frozen state were sent to the analytical facility in shipments through internal courier on 31 December 2013. The plasma samples of period I were stored at clinical facility at ≤ -15°C for 27 days (05 December 2013 to 31 December 2013). The plasma samples of period II were stored at clinical facility at ≤ -15°C for 13 days (19 December 2013 to 31 December 2013).

Standard FDA Meal Used?	No The meal satisfies caloric requirements per the general guidance.

Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study						
Ingredients		**Amount (g) Raw Weight**	**Energy (kcal)**	**Protein (kcal)**	**Fat (kcal)**	**Carbohydrate (kcal)**
SANDWICH						
Omelet	2 Eggs	120	208.00	64.00	144.00	0.00
	Onion	20	10.24	1.44	0.00	8.80
	Green Chilies	5	1.20	0.60	0.00	0.60
Boiled Potato (Hash brown)		120	116.00	8.00	0.00	108.00
2 Slices of bread (Toasted)		48	116.60	14.00	9.00	93.60
Goat meat		24	28.30	20.56	7.74	0.00
Butter		30	216.00	0.00	216.00	0.00
Cheese		30	104.25	28.92	67.77	7.56
MILK						
Milk (cow's)		240	166.00	32.00	90.00	44.00
Sugar		5	20.00	0.00	0.00	20.00
TOTAL (K calories)			**986.59**	**169.52**	**534.51**	**282.56**
PERCENTAGE			**100.00**	**17.18**	**54.18**	**28.64**

Comments on Study Design:

The study design is acceptable.

1.9.2.2 Clinical Results

Table 17. Demographics Profile of Subjects Completing the Bioequivalence Study

Study Number PKD 13 460			
		Treatment Groups	
		Test Product N = 32	Reference Product N = 32
Age (Years)	Mean ± SD Range	31.3 +/- 7.16 21 – 43	31.3 +/- 7.16 21 – 43
Age Groups	< 18 18-40 41-64 65-75 >75	0 (0.0%) 28 (87.5 %) 4 (12.5 %) 0 (0.0%) 0 (0.0%)	0 (0.0%) 28 (87.5 %) 4 (12.5 %) 0 (0.0%) 0 (0.0%)
Sex	Male Female	32 (100.0%) 0 (0.0%)	32 (100.0%) 0 (0.0%)
Race	Asian Black Caucasian Hispanic Other	32 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	32 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
BMI	Mean ± SD Range	21.31 ± 2.256 18.6 – 24.9	21.31 ± 2.256 18.6 – 24.9
Other Factors		N/A	N/A

Table 18. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
--			

Table 19. Study Adverse Events, Fed Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Number: PKD_13_460	
MedDRA System Organ Class Preferred Term	Test	Reference
Investigations[1]		
Aspartate aminotransferase increased	1 (50.0)	
Alanine aminotransferase increased	1 (50.0)	
Total	**2 (100.0)**	

[1] Since no biochemistry assessment (AST, ALT) was done after screening until check-out of period II, these adverse events were considered to be emerged from both the formulations.

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
--				

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

- There is no substantial difference between the test and reference product for adverse event profile.
- Two subjects experienced 3 post dose adverse events in this study. Given no biochemistry assessment (AST, ALT) was done after screening until check-out of period II, these adverse events were considered to be possibly related to both the formulations.

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee?
No deaths and serious adverse events were reported during the study.

Are there any other safety concerns based on the adverse event profile?
No.

Table 20. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
--		

Comments:

No dropout and protocol deviation were reported in the fed study.

1.9.2.3 Bioanalytical Results

Table 21. Sample Analysis Calibration and Quality Control

14.3Study# PKD_13_460 (pivotal fed) - Iloperdone

Bioequivalence Study Number: PKD_13_460										
Analyte	**Iloperidone**									
Parameter	**Standard Curve Samples**									
Concentration (pg/mL)	21.2	21.2	42.3	193.1	448.4	1145.9	1644.1	1992.8	2491.0	2491.0
Inter Day Precision (% CV)	5.4	5.0	4.1	1.6	1.5	1.3	1.6	1.0	1.7	1.3
Inter Day Accuracy (% Actual)	99.2	101.1	98.5	103.5	100.0	98.9	100.5	100.2	99.2	98.9
Linearity	0.9983 to 0.9998									
Linearity range	21.2 to 2491.0									

(pg/mL)	
Limit of Quantitation (pg/mL)	21.2

Study# PKD_13_460 (pivotal fed) - Iloperdone

Bioequivalence Study Number: PKD_13_460					
Analyte	**Iloperidone**				
Parameter	**Quality Control Samples**				
Concentration (pg/mL)	62.5	187.6	650.3	1225.5	2050.8
Inter Day Precision (% CV)	4.1	11.2	2.0	1.8	1.7
Inter Day Accuracy (% Actual)	101.9	103.5	99.4	98.4	98.9

Study# PKD_13_460 (pivotal fed) - P88 Metabolite

Bioequivalence Study Number: PKD_13_460										
Analyte	**P88 Metabolite**									
Parameter	**Standard Curve Samples**									
Concentration (pg/mL)	15.4	15.4	30.8	147.7	344.7	861.7	1255.7	1551.1	1994.3	1994.3
Inter Day Precision (% CV)	5.0	4.9	5.5	2.6	1.6	2.0	2.2	1.6	1.4	1.8
Inter Day Accuracy (% Actual)	99.7	101.6	97.0	102.0	100.2	99.9	100.6	100.2	99.6	99.2
Linearity	0.9954 to 0.9997									
Linearity range (pg/mL)	15.4 to 1994.3									
Limit of Quantitation (pg/mL)	15.4									

Study# PKD_13_460 (pivotal fed) - P88 Metabolite

Bioequivalence Study Number: PKD_13_460					
Analyte	**P88 Metabolite**				
Parameter	**Quality Control Samples**				
Concentration (pg/mL)	45.9	137.8	521.4	993.1	1638.7
Inter Day Precision (% C.V.)	4.7	3.1	2.8	2.0	2.6
Inter Day Accuracy (% Actual)	99.3	99.5	96.6	98.8	99.3

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

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

Table 22. SOP's Dealing with Sample Analysis

SOP No (b) (4)	Effective Date of SOP	SOP Title
		Estimation of Iloperidone and its P88 Metabolite in human K2EDTA plasma using Ultra High Performance Liquid Chromatography Method with Tandem mass spectrometry- (b) (4)
		Evaluation of stability of drug(s) in biological matrix and solutions.
		Bioanalytical Method Validation
		Verification of Chromatograms , Peak Integration and Chromatographic Acceptance Criteria
		Repeat sample(s) identification, re-analysis and reporting of final concentration
		Procedure for detection of statistical outliers
		Chromatographic Analysis of Study Sample
		Preparation, identification and acceptance criteria of stock solutions, calibration standards, quality control samples.
		Identification and reanalysis of incurred samples
		Partial Bioanalytical Method Validation

Comments:

- The calibration was produced from eight nominal concentration plasma samples over the linear ranges of 21.2pg/mL to 2491.0pg/mL for Iloperidone and 15.4pg/mL to 1994.3pg/mL for P88 Metabolite. The firm used duplicated samples for lowest and highest calibration standards, according SOP (b) (4)
- The calibration and quality control data for the sample analysis are acceptable.
- The firm conducted the Incurred Sample Reanalysis (ISR) in accordance with the SOP, and demonstrated that 99.4% (159 out of 160) of samples for iloperidone were within the acceptance range of ± 20 % for the percent difference between the original and reanalyzed values.

1.9.2.4 Pharmacokinetic Results

Is there a Tmax difference between T and R	No
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	No
Is sampling time adequate?	Yes

Overall Comment:

The fed study is adequate.

Table 23. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study (Firm-submitted Data in Firm's Format)

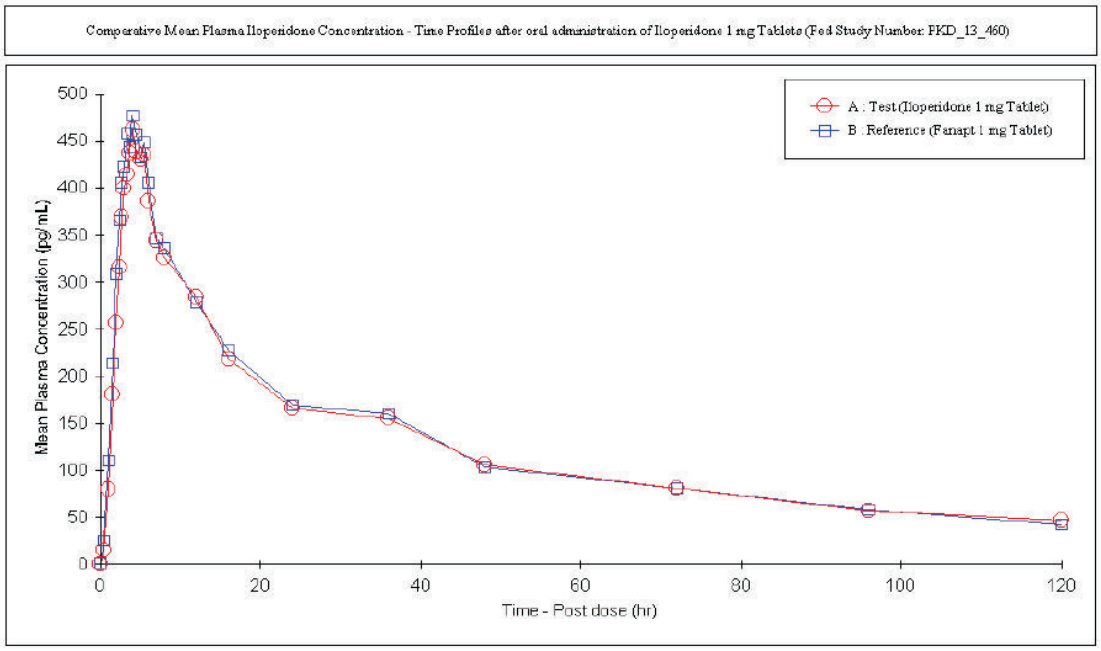
Least Square Means (pg/mL)

Collection Time (hr.)	TestLSM	RefLSM	Significance[#]	p Value
0.000	0.0000	0.7250	None	0.3253
0.500	14.7438	25.3063	None	0.2655
1.000	79.1937	109.6906	None	0.2251
1.500	180.1500	213.7156	None	0.4129
2.000	256.4062	309.0250	None	0.2208
2.333	315.5531	365.4500	None	0.1834
2.667	369.2562	404.9438	None	0.3098
3.000	399.4406	421.7906	None	0.4204
3.333	414.8687	457.8969	< 0.05	0.0464
3.667	436.6875	444.1875	None	0.6209
4.000	462.1625	476.3688	None	0.2175
4.500	438.0719	456.0000	None	0.2365
5.000	430.2156	432.0969	None	0.9104
5.500	435.1812	448.5969	None	0.4275
6.000	385.8125	405.7719	None	0.1823
7.000	343.7375	346.3344	None	0.8154
8.000	325.9250	335.5438	None	0.3584
12.000	283.6813	278.3406	None	0.5343
16.000	217.4219	227.1656	None	0.1502
24.000	165.5500	168.8938	None	0.5578
36.000	154.9406	159.7813	None	0.3687
48.000	105.1625	103.0594	None	0.5880
72.000	80.0319	80.6781	None	0.8358
96.000	56.5976	57.5843	None	0.7120
120.000	46.3687	41.9406	None	0.0839

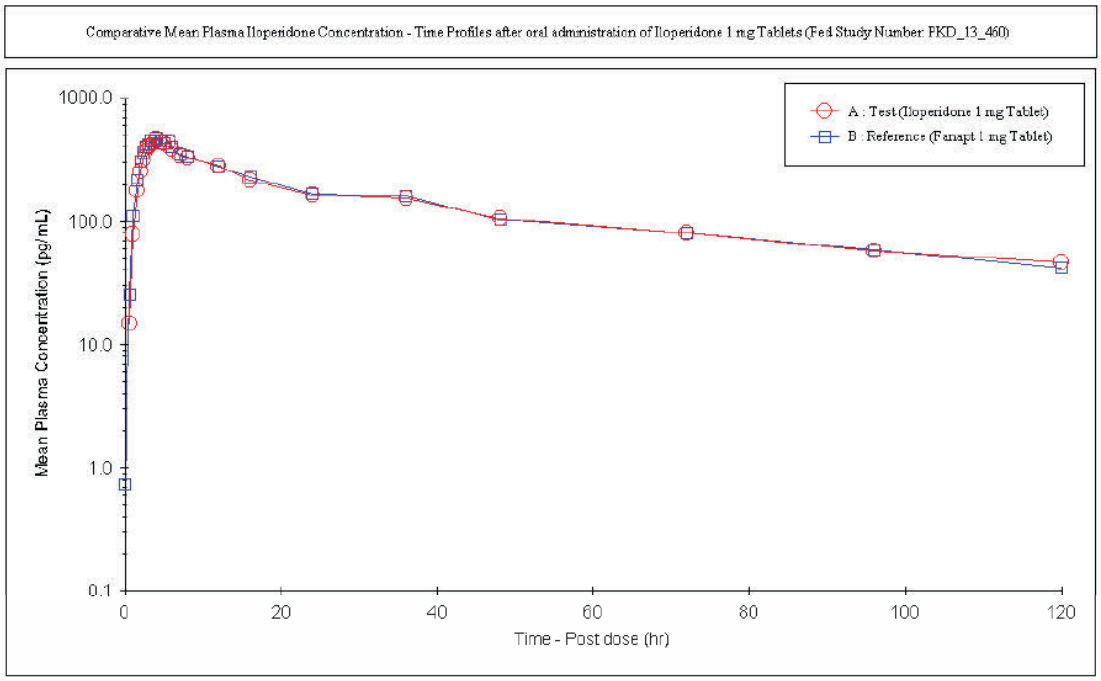
[#]Results of the statistical evaluation by ANOVA (α =0.05) for the hypothesis of equal treatment effects. None indicate that no statistical significant difference was detected between treatment means (P >0.05) at the sampling time evaluated.

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

Linear plot of mean plasma concentration-time profile of Iloperidone (N=32):



Semi Logarithmic Plot of Mean Plasma Concentration-time profile of Iloperidone (N=32):



1.9.3 Pilot Fasting Study

1.9.3.1 Study Design

Study Information

Study Number	2013-3306
Study Title	A Single-Dose, Comparative Bioavailability Study of Three Formulations of Iloperidone 1 mg Tablets under Fasting Conditions
Clinical Site (Name & Address)	Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6 Phone: (416) 759-4111 Fax: (416) 759-2869
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C), Email: echen@pharmamedica.com
Dosing Dates	September 09, 2013; September 18, 2013 and September 27, 2013
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	October 02, 2013 to October 07, 2013
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	28 days, -35°C to -15°C

Product Information

Product	Test A	Test B	Reference
Treatment ID	A	B*	C
Product Name	Iloperidone 1 mg Tablets	Iloperidone 1 mg Tablets	Fanapt® 1 mg Tablets
Manufacturer	(b) (4)		
Batch/Lot No.	781983	781984	GVSB
Manufacture Date	07/2013	07/2013	N/A
Expiration Date	N/A	N/A	04/2013
Strength	1 mg	1 mg	1 mg
Dosage Form	Tablets	Tablets	Tablets
Bio-batch Size	(b) (4)		N/A
Production Batch Size			N/A
Potency	97.9%	100.6%	100.5%

Content Uniformity (mean, %CV)	Not submitted	L1=3.5<15	N/A
Dose Administered	1 x 1 mg	1 x 1 mg	1 x 1 mg
Route of Administration	Oral	Oral	Oral

N/A: Not Applicable
*The formulation B (lot# 781984) was selected for the pivotal studies

1.9.3.2 Clinical Results

Demographics Profile of Subjects Completing the Bioequivalence Study

Study No: 2013-3306			
		Treatment Groups	
		Test Product N = 15	**Reference Product N = 15**
Age (years)	Mean ± SD Range	41 ± 12 24 - 57	41 ± 12 24 - 57
Age Group	< 18 18 - 40 41 - 64 65 - 75 > 75	0 (0.0%) 7 (46.7%) 8 (53.3%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 7 (46.7%) 8 (53.3%) 0 (0.0%) 0 (0.0%)
Sex	Male Female	7 (46.7%) 8 (53.3%)	7 (46.7%) 8 (53.3%)
Race	Asian Black Caucasian Hispanic Other	2 (13.3%) 4 (26.7%) 9 (60.0%) 4 (26.7%) 0 (0.0%)	2 (13.3%) 4 (26.7%) 9 (60.0%) 4 (26.7%) 0 (0.0%)
BMI	Mean ± SD Range	26.9 ± 2.5 22.4 - 30.0	26.9 ± 2.5 22.4 - 30.0
Other Factors		N/A	N/A

Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
--			

Incidence of Adverse Events in Individual Studies
Study # 2013-3306 (pilot fasted)

System Organ Class Term Preferred Term	Reported Incidence by Treatment Groups		
	Fasted Bioequivalence Study Study No: 2013-3306		
	Test A N = 15	**Test B** N = 15	**Ref C** N = 15
Cardiac disorders			
Bradycardia	0 (0.0%)	1 (6.7%)	0 (0.0%)
Eye disorders			
Eye irritation	1 (6.7%)	1 (6.7%)	0 (0.0%)
Gastrointestinal disorders			

Abdominal discomfort	1 (6.7%)	0 (0.0%)	0 (0.0%)
Abdominal distension	1 (6.7%)	0 (0.0%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	0 (0.0%)	1 (6.7%)
Constipation	3 (20.0%)	1 (6.7%)	0 (0.0%)
Flatulence	1 (6.7%)	1 (6.7%)	0 (0.0%)
Nausea	0 (0.0%)	0 (0.0%)	1 (6.7%)
Metabolism and nutrition disorders			
Decreased appetite	1 (6.7%)	1 (6.7%)	0 (0.0%)
Nervous system disorders			
Dizziness	1 (6.7%)	0 (0.0%)	0 (0.0%)
Headache	1 (6.7%)	1 (6.7%)	2 (13.3%)
Presyncope	0 (0.0%)	1 (6.7%)	0 (0.0%)
Somnolence	10 (66.7%)	11 (73.3%)	11 (73.3%)
Respiratory, thoracic and mediastinal disorders			
Nasal congestion	1 (6.7%)	0 (0.0%)	1 (6.7%)
Vascular disorders			
Hypertension	0 (0.0%)	1 (6.7%)	1 (6.7%)
Hypotension	1 (6.7%)	0 (0.0%)	1 (6.7%)
*Total	11 (73.3%)	12 (80.0%)	12 (80.0%)

*Total and percentage count is based on each subject who experienced at least one AE in each of the treatments.

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
--				

Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
--		

1.9.3.3 Bioanalytical Results

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses
Iloperidone

Bioequivalence Study No. Bioequivalence Study No. 2013-3306								
Analyte	**Iloperidone**							
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	5.00	10.0	25.0	60.0	150.0	350.0	800.0	1250.0
Inter day Precision (%CV)	3.5	2.8	2.3	1.2	2.3	2.0	1.1	0.9

Inter day Accuracy (%Actual)	106.2	100.0	95.6	101.0	98.0	98.3	100.9	100.2
Linearity	0.9997 to 1.0000							
Linearity Range (pg/mL)	5.00 to 1250							
Sensitivity/LOQ (pg/mL)	5.00							

Bioequivalence Study No. Bioequivalence Study No. 2013-3306			
Analyte	**Iloperidone**		
Parameter	**Quality Control Samples**		
Concentration (pg/mL)	15.0	625	1000
Inter day Precision (%CV)	3.1	3.1	2.2
Inter day Accuracy (%Actual)	104.7	101.9	100.9

P88 Metabolite

Bioequivalence Study No. 2013-3306								
Analyte	**P88 Metabolite**							
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	5.00	10.0	25.0	60.0	150.	350.	800.	1250.
Inter day Precision (%CV)	3.4	2.5	1.3	2.9	2.3	2.1	1.1	1.1
Inter day Accuracy (%Actual)	102.8	102.0	97.2	101.0	97.3	98.6	101.8	99.6
Linearity	0.9997 to 0.9999							
Linearity Range (pg/mL)	5.00 to 1250							
Sensitivity/LOQ (pg/mL)	5.00							

Bioequivalence Study No. 2013-3306			
Analyte	**P88 Metabolite**		
Parameter	**Quality Control Samples**		
Concentration (pg/mL)	15.0	625	1000
Inter day Precision (%CV)	2.5	3.0	2.7
Inter day Accuracy (%Actual)	101.3	100.6	100.6

1.9.3.4 Pharmacokinetic Results

Drug: Iloperidone No of subjects completed = 7 males and 8 females, Dose 1 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Test A Batch # 781983						
Parameter	**Test A**	**N**	**Ref**	**N**	**Ratio (%)**	**90% C.I.**
Iloperidone						
AUCo-t (pg.h/mL)	10801.20	15	10549.47	15	102.39	95.43 - 109.85
AUCo-∞ (pg.h/mL)	15170.26	15	15063.82	14	100.71	94.23 - 107.63

Cmax (pg /mL)	786.00	15	787.13	15	99.86	87.99 - 113.33
P88 Metabolite						
AUCo-t (pg.h/mL)	14643.56	15	14929.23	15	98.09	93.03 - 103.42
AUCo-∞ (pg.h/mL)	19427.48	15	20886.92	15	93.01	88.30 - 97.98
Cmax (pg /mL)	467.60	15	462.44	15	101.12	94.47 - 108.23
Test B Batch # 781984						
Parameter	**Test B**	**N**	**Ref**	**N**	**Ratio (%)**	**90% C.I.**
Iloperidone						
AUCo-t (pg.h/mL)	10989.29	15	10549.47	15	104.17	97.10 - 111.76
AUCo-∞ (pg.h/mL)	15312.05	15	15063.82	14	101.65	95.11 - 108.64
Cmax (pg /mL)	793.39	15	787.13	15	100.79	88.81 - 114.39
P88 Metabolite						
AUCo-t (pg.h/mL)	15278.68	15	14929.23	15	102.34	97.07 - 107.90
AUCo-∞ (pg.h/mL)	21032.01	15	20886.92	15	100.69	95.59 - 106.07
Cmax (pg /mL)	486.79	15	462.44	15	105.27	98.34 - 112.67

Reviewer's Comments:

- The firm conducted a pilot fasting study to study the effect of the PSD of API on the BE using batches 781983 with PSD of D(0.9) (b) (4) and 781984 DS with PSD of D(0.9) (b) (4) The study results indicated that both batches 781983 and 781984 met the BE criteria. The firm conducted the pivotal studies with batch 781984, which contains micronized Iloperidone D(0.9) (b) (4)
- The firm did not provide the intensity of the adverse events in the pilot study including the severity/intensity of the AEs (i.e., mild, moderate, severe, serious etc.). The firm will be asked to provide this information.

1.10 Formulation Data

Ingredient	Amount (mg) / Tablet						
	1 mg*	2 mg	4 mg	6mg	8 mg	10 mg	12 mg
Iloperidone	1.000	2.000	4.00	6.00	8.00	10.00	12.00
Microcrystalline Cellulose, NF/Ph.Eur	(b) (4)						
Lactose Monohydrate, NF/Ph.Eur	(b) (4)						
Collodial Silicon Dioxide, NF/ Ph.Eur							
Crospovidone, NF,	(b) (4)						
Magnesium Stearate, NF/ Ph.Eur							
Purified Water, USP/ Ph.Eur	(b) (4)						
Total							

(b) (4)

* The strength used for the BA/BE studies
** The formulations are fully proportional

(b) (4)

[5] DARRTS, NDA 207098, CHIDAMBARAM, NALLAPERUM 10/12/2004 REV-QUALITY-03(General Review) Archive

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

Reviewer's Comments:

- The formulations of 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg are proportionally similar to the 1 mg test product which underwent BE testing.
- The formulations are adequate.

1.11 Dissolution Data (Applicable if there are waiver requests)

Dissolution Review Path	GDRP, ANDA-207098-ORIG-1, Biopharmaceutics Primary Review 207098D060214.doc Review Sam Chan 13-Jan-2015

Table 24. Dissolution Data

5.1 Study # 2013-3306 (pilot fasted)

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1M HCl (b) (4)
	Volume:	500 mL (b) (4)
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NL T (b) (4) % (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Study Ref No.	**Testing Date**	**Product ID\Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						5 min	10 min	15 min	30 min	45 min	60 min	
Study Report #:	August 13, 2013	Test Product – 781983 (Mfg date – July, 2013)	1 mg Tablet	12	Mean	83	87	95	97	98	99	
					Range	(b) (4)						
					%CV	13.05	13.01	3.42	2.04	1.41	1.33	Batch Analysis Section 3.2.P.5.4
Study Report #:	August 13, 2013	Test Product – 781984 (Mfg date – July, 2013)	1 mg Tablet	12	Mean	102	102	102	103	103	103	
					Range	(b) (4)						
					%CV	2.51	1.32	1.21	1.11	1.05	1.17	
Study	August	Reference Product –	1 mg	12	Mean	98	98	98	99	99	99	

Report #:	18, 2013	GVSB (Exp date–April, 2014)	Tablet		Range	[redacted] (b) (4)						
					%CV	4.64	1.47	1.08	0.91	1.04	1.07	

5.2 Studies # PKD_13_459 & PKD_13_460 (pivotal fasted & fed)

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1M HCl [redacted] (b) (4)
	Volume:	500 mL [redacted] (b) (4)
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NL T [redacted] (b) (4) % (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						5 min	10 min	15 min	30 min	45 min	60 min	
Study Report #:	August 13, 2013	Test Product – 781984 (Mfg date – July, 2013)	1 mg Tablet	12	Mean	102	102	102	103	103	103	Batch Analysis Section 3.2.P.5.4
					Range	[redacted] (b) (4)						
					%CV	2.51	1.32	1.21	1.11	1.05	1.17	
Study Report #:	August 18, 2013	Reference Product – GVSB (Exp date–April, 2014)	1 mg Tablet	12	Mean	98	98	98	99	99	99	
					Range	[redacted] (b) (4)						
					%CV	4.64	1.47	1.08	0.91	1.04	1.07	

9 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

Please comment on whether dissolution data are adequate to support waiver requests.	NO

Overall Comment:

- The dissolution review is reviewed separately and the result is inadequate.[1]
- Per dissolution review, the firm conducted dissolution testing using its own proposed method [500 ml 0.1 N HCl (b) (4) @ 37 ± 0.5°C, USP apparatus II (b) (4) at 50 rpm]. (b) (4) The firm was asked to conduct dissolution testing on twelve (12) dosage units of unexpired batches of each test and reference product using the FDA-recommended method [500 ml 0.1 N HCl @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm].[1]
- Given the dissolution data is not acceptable in the current application, the dissolution data are not adequate to support the waiver requests.

1.12 OSIS History

Clinical Site:
Sun Pharmaceutical Industries Ltd
Clinical Pharmacology Unit,
Sun Pharmaceutical Industries Ltd.
Tandalja,
Vadodara – 390 020 (India)
Clinical period: 12/3/2013 – 12/24/2013

Application #	Inspection type	Inspection	Study Period	Outcome	relevant
NDA 204417	routine	(b) (4)	5/3/10 to 9/10/10	NAI	Yes
(b) (4)					
NDA 205583	routine		5/28/2012 – 8/16/2012	VAI	Yes
ANDA 205078	routine		9/5/12 – 9/17/12	NAI	Yes

Reviewer's Comments:

- There is no pending inspection for this site.
- The outcome of the most recent relevant inspection is NAI.
- Based on evaluation of the submitted data, the OSI inspection of the clinical site for the current ANDA is not necessary. The studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The OSI inspection status for the current ANDA is considered complete at this time.

(b) (4)

(b) (4)

Application #	Inspection type	Inspection period	Study Period	Outcome	relevant
ANDA 202635	routine	(b) (4)		NAI	No
ANDA 203263	routine			VAI	No
NDA 204417	routine			NAI	Yes
NDA 205583	routine			VAI	Yes

Reviewer's Comments:

- There is no pending inspection for this site.
- The outcome of the most recent relevant inspection is VAI.

(b) (4)

DBIII Reviewer's Comment:

The protocol deviations of the current BE studies do not contain any similar violation. Therefore, the finding is not applicable to current BE studies.

(b) (4)

OSIS Comments:

DBIII Reviewer's Comment:
There were no study sample reintegration reported in current BE studies. Therefore, the finding is not applicable to current BE studies.

- Based on evaluation of the submitted data, the OSI inspection of the analytical site for the current ANDA is not necessary. The studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The current ANDA reviewer determined that the findings of the OSI inspection identified for NDA 205583 are not expected to impact the BE study outcomes of the current ANDA. The OSI inspection status for the current ANDA is considered complete at this time.

1.13 Consult Reviews

N/A

1.14 Attachments

N/A

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 207098

APPLICANT: Taro Pharmaceutical U.S.A., Inc.

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

The Division of Bioequivalence has completed its review and has identified the following deficiencies:

1. Please provide the details of all adverse events (AEs) reported in the pilot study (2013-3306) including the severity/intensity of the AEs (i.e., mild, moderate, severe, serious etc.).
2. Your waiver requests for the 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg strengths are not considered at this time due to inadequate dissolution testing data for all strengths of the test and reference products. (b) (4) Please submit additional dissolution testing data on twelve (12) dosage units of unexpired batches of each test and reference product using the following FDA-recommended method (with conventional USP dissolution vessels), to support the waiver requests of the lower strengths of the test product, as well to establish a regulatory dissolution method and specifications for quality control purposes.

Apparatus	II (paddle)
Speed of Rotation	50 rpm
Medium	0.1N HCl
Volume	500 mL
Recommended Sampling Times	5, 10, 15, 30, 45 and 60 minutes

3. If necessary, please develop a discriminating and reproducible dissolution method, using conventional USP apparatuses (b) (4) for the purpose of comparing dissolution profiles between strengths of the test and reference products in support of your waiver requests of the lower strengths.

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}

Hoainhon N. Caramenico, M.S., M.S.
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

1.15 Outcome Page

ANDA: 207098

Reviewer: Chang, Yang **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
25793	6/2/2014	Bioequivalence Study (REGULAR)	Fasting Study	1	1
25793	6/2/2014	Bioequivalence Study (REGULAR)	Fed Study	1	1
25793	6/2/2014	Bioequivalence Study (REGULAR)	Fasting Study	1	1
25793	6/2/2014	Other (REGULAR)	Dissolution-Based Waiver	1	1
25793	6/2/2014	Other (REGULAR)	Dissolution-Based Waiver	1	1
25793	6/2/2014	Other (REGULAR)	Dissolution-Based Waiver	1	1
25793	6/2/2014	Other (REGULAR)	Dissolution-Based Waiver	1	1
25793	6/2/2014	Other (REGULAR)	Dissolution-Based Waiver	1	1
25793	6/2/2014	Other (REGULAR)	Dissolution-Based Waiver	1	1
25793	6/2/2014	Quality Assessment	Quality	4	4
				Total:	15

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	207098
Drug Product Name	Iloperidone Tablets
Strength (s)	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg
Applicant Name	Taro Pharmaceutical Industries Ltd.
Applicant Address	14 Hakitor Street, Haifa Bay, Israel, 2624761
US Agent Name and the mailing address	Taro Pharmaceuticals U.S.A. Inc. (Kavita Srivastava, Executive Director, Regulatory Affairs), 3 Skyline Drive, Hawthorne, NY 10532
US Agent's Telephone Number	914-345-9001 (b) (6)
US Agent's Fax Number	914-593-0078
Original Submission Date(s)	06/02/2014
Submission Date(s) of Amendment(s) Under Review	
Reviewer	Sam Chan
Dissolution Method	**INADEQUATE**
OVERALL REVIEW RESULT	**INADEQUATE**

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method, but there is an FDA-recommended dissolution method for Iloperidone Tablets. The firm conducted dissolution testing using its own proposed method (500 ml 0.1 N HCl (b) (4) @ 37 ± 0.5°C, USP apparatus II (b) (4) at 50 rpm) only. (b) (4)

The testing compared the applicant's Iloperidone Tablets, (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg), to (b) (4) Fanapt® (iloperidone) tablets, (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg).

The firm should conduct dissolution testing on twelve (12) dosage units of unexpired batches of each test and reference product using the following FDA-recommended method:

500 ml 0.1 N HCl @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm.

In addition there are deficiencies related to dissolution method effective date, and BE Summary Table 5.

The dissolution testing conducted is **incomplete**.

II. DISSOLUTION REVIEW

II.1 Submission Content Checklist

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

II.2 Dissolution Method As Posted on the FDA Website (if any)

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

II.3 USP Method (if any)

II.4 Summary of In Vitro Dissolution Data

Provide dissolution data for all strengths (test and reference).

Dissolution Conditions	**Apparatus:**	USP 2 (paddles)
	Speed of Rotation:	50 rpm
	Medium:	0.1M HCl (b) (4)
	Volume:	500 mL (b) (4)
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	NL T (b) (4) % (Q) of the labeled amount is dissolved in 30 min	
Dissolution Testing Site (Name, Address)	Taro Pharmaceutical Industries Ltd. 14 Hakitor Street Haifa Bay 2624761, Israel	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						5 min	10 min	15 min	30 min	45 min	60 min	
Study Report #:	August 13, 2013	Test Product – 781984 (Mfg date – July, 2013)	1 mg Tablet	12	Mean	102	102	102	103	103	103	
					Range	(b) (4)						
					%CV	2.51	1.32	1.21	1.11	1.05	1.17	Batch Analysis Section 3.2.P.5.4
Study Report #:	August 18, 2013	Reference Product – GVSB (Exp date–April, 2014)	1 mg Tablet	12	Mean	98	98	98	99	99	99	
					Range	(b) (4)						
					%CV	4.64	1.47	1.08	0.91	1.04	1.07	

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Dissolution Method SOP effective at the time of testing (Yes/No)	No (May 19. 2014)
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.	N/A (Only provide month of manufacturer)
Was the reference product expired at the time of dissolution testing (Yes/No)	No
Comments on the variability of the dissolution data	The variability of the data is adequate
For two-stage dissolution testing, comment on the method of medium change from acid stage to buffer stage.	N/A

III. Reviewer's Comments for Dissolution Testing

1. There is no USP method, but there is an FDA-recommended dissolution method for Iloperidone Tablets. The firm conducted dissolution testing using its own proposed method (500 ml 0.1 N HCl (b) (4) @ 37 ± 0.5°C, USP apparatus II (b) (4) at 50 rpm) only. (b) (4)

2. The testing compared the applicant's Iloperidone Tablets, (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg), to (b) (4) Fanapt® (iloperidone) tablets, (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg).

3. The firm should conduct dissolution testing on twelve (12) dosage units of unexpired batches of each test and reference product using the following FDA-recommended method:
   500 ml 0.1 N HCl @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm.

4. The Bioequivalence (BE) Summary Table 5 for 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg for the dissolution data could not be located in the submission. The firm should provide Bioequivalence (BE) Summary Table 5, for the dissolution data of all the strengths.

5. The dissolution method was not in effect at the time of dissolution testing. The firm reported using the Analytical Method (SOP) (Taro Research Institute (b) (4) for conducting dissolution testing. All the reported dissolution testing was conducted prior to the effective date: May 19, 2014. For future submissions, the firm will be requested to submit dissolution data using an effective method.

IV. Deficiency Comment for Dissolution Testing

1. The dissolution testing is incomplete. The firm conducted dissolution testing using its own proposed method (500 ml 0.1 N HCl (b) (4) @ 37 ± 0.5°C, USP apparatus II (b) (4) at 50 rpm) only.

2. The firm should conduct dissolution testing on twelve (12) dosage units of unexpired batches of each test and reference product using the following FDA-recommended method:
   500 ml 0.1 N HCl @ 37.0 ± 0.5°C, USP apparatus II at 50 rpm.

3. The Bioequivalence (BE) Summary Table 5 for 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg for the dissolution data could not be located in the submission. The firm should provide Bioequivalence (BE) Summary Table 5, for the dissolution data of all the strengths.

4. The dissolution method was not in effect at the time of dissolution testing. The firm reported using the Analytical Method (SOP) (Taro Research Institute [redacted] (b) (4) for conducting dissolution testing. All the reported dissolution testing was conducted prior to the effective date: May 19, 2014. For future submissions, the firm will be requested to submit dissolution data using an effective method in place.

V. Dissolution Recommendations

The in vitro dissolution testing conducted by Taro Pharmaceutical Industries Ltd. on its test product, Iloperidone Tablets, 1 mg (lot# 781984), 2 mg (lot# 782085), 4 mg (lot# 782086), 6 mg (lot# 782087), 8 mg (lot# 782088), 10 mg (lot# 782089) and 20 mg (lot# 782090) comparing it to [redacted] (b) (4) Fanapt® (iloperidone) tablets, 1 mg (lot# GVSB), 2 mg (lot# KZDD), 4 mg (lot# KWDX), 6 mg (lot# KKTB), 8 mg (lot# KZDK), 10 mg (lot# MGSC) and 20 mg (lot# MDGD), respectively, is **inadequate** due to the deficiencies cited above.

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

ANDA: 207098

APPLICANT: Taro Pharmaceutical Industries Ltd.

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

The Division of Bioequivalence (DB) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. DB will review the bioequivalence studies and waiver requests later. The following deficiencies have been identified:

1. Your dissolution testing is not acceptable. (b) (4) Please conduct dissolution testing on twelve (12) dosage units of unexpired batches of each test and reference product using the following FDA-recommended method:

USP Apparatus	II (paddle)
Rotation speed	50 rpm
Medium	0.1 N HCl
Volume	500 ml
Temperature	37.0 ± 0.5°C
Sampling Times	5, 10, 15, 30, 45 and 60 minutes

2. The Bioequivalence (BE) Summary Table 5 for 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths, for the dissolution data could not be located in the submission. Please submit Bioequivalence (BE) Summary Table 5, for the dissolution data of all the strengths.

3. The dissolution method was not in effect at the time of dissolution testing. You reported using the Analytical Method (Taro Research Institute (b) (4) for conducting dissolution testing. All the reported dissolution testing was conducted prior to the effective date: May 19, 2014. For future submissions, please submit dissolution data using an effective method.

Sincerely yours,

{See appended electronic signature page}

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

VI. OUTCOME

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod