

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-192

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name): Iloperidone
PRODUCT (Brand Name):
DOSAGE FORM: Tablets
DOSAGE STRENGTHS: 1mg, 2mg, 4mg, 6mg, 8mg,
10mg, 12mg
NDA: 22-192
NDA TYPE: New Molecular Entity
SUBMISSION DATE: November 6, 2008
SPONSOR: Vanda Pharmaceuticals
REVIEWER: Andre Jackson

REVIEW OF NDA RESPONSES

The Agency's Not Approvable (NA) action letter of July 25, 2008 to the sponsor conveyed two Comments from OCP. These were:

- (1) The hepatic impairment study was inconclusive because the exposure for mild subjects was greater than that for moderately impaired subjects, and the sponsor was requested to repeat the study.
- (2) The sponsor should investigate the possible interaction of iloperidone and P-Gp.

Since this was a NA letter the above Comments were not conveyed as Phase IV commitments but rather as regular clinical pharmacology comments with the understanding that both items could be fulfilled before the approval of the drug. Also, as is generally the case, the NA letter did not forward the

Dissolution method and specification which had been completed in OCP's review.

The sponsor met with the Agency on September 10, 2008, and discussed the comments that they had received from all disciplines in the letter. The sponsor sent in their Responses to the NDA on November 6, 2008 also addressing the two OCP Comments. The firm's responses has satisfactorily addressed the clinical issues; therefore, the clinical division is planning on issuing an Action letter.

OCP in this review addresses the two earlier comments (viz., hepatic impairment, and transporter interaction), since they have now become Phase IV commitments (see Items 1 and 2 below), and, restating the Dissolution method and specification for convey to the sponsor (see Item 3 below). Finally, the latest version of the Labelling received from the clinical division has been compared to the one is OCP's review, and it is acceptable (see Item 4 below; Appendix I)

Item 1

A meeting was held with the firm to discuss Hepatic Study CIL0522A0103 were discussed. The firm agreed to repeat the study in a moderately impaired group, comparing them to normals in the same study, as a post-marketing commitment.

Vanda will also honor FDA's request to submit the genotyping information for the extensive metabolizers used in this study.

Until the new hepatic data is provided to FDA, Vanda will agree to the following labeling in the package insert:

┌

b(4)

b(5)

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Item 2

In Vitro Interaction of Iloperidone and P-Glycoprotein (P-Gp) was discussed in the meeting with FDA and Vanda has agreed to perform an in vitro interaction study as a post-marketing commitment.

Comment on Phase IV Commitments (Items 1 and 2 above):

The fulfilling of both items mentioned above as Phase IV commitments is acceptable to OCP.

The timeline for completion is as follows:

- (1) Hepatic Impairment Study -- 2 years after receipt of Action letter
- (2) In Vitro P-Gp Transporter Study – 6 months after receipt of Action letter.

Item 3

Dissolution Method and Specification (from OCP's review of July 10, 2008) – for convey to the Sponsor:

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

Apparatus 2 (rotating paddle)
500 ml 0.1 N HCl
50 rpm rotation speed.
Q= — in 30 minutes

b(4)

Item 4

Labelling – see Appendix I

SIGNATURES

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28 pgs of draft labeling has been removed
after this page.

28 Page(s) Withheld

       Trade Secret / Confidential (b4)

X Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

Andre Jackson
1/15/2009 07:36:26 AM
BIOPHARMACEUTICS

Raman Baweja
1/15/2009 03:34:54 PM
BIOPHARMACEUTICS

Mehul Mehta
1/15/2009 04:13:49 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

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PRODUCT (Brand Name):

DOSAGE FORM: Tablets

DOSAGE STRENGTHS: 1mg, 2mg, 4mg, 6mg, 8mg,
10mg, 12mg

NDA: 22-192

NDA TYPE: New Molecular Entity

SUBMISSION DATE: September 27, 2007

SPONSOR: Vanda Pharmaceuticals

REVIEWER: Andre Jackson

REVIEW OF NDA

EXECUTIVE SUMMARY

The firm is seeking approval for an oral tablet of iloperidone at dosage strengths of 1mg, 2mg, 4mg, 6mg, 8mg, 10mg, and 12 mg with a recommended target dose of 12 mg/day. The drug is metabolized by CYP2D6 which catalyzes hydroxylation of the acyl group to form metabolite P94 which is converted to P95. There have been shown to be poor, intermediate, extensive (regarded as the normal phenotype) and ultrarapid metabolizers. However there are other routes of metabolism not involving CYP2D6. CYP3A4 causes demethylation to metabolite P89 which is inactive. P88 is generated by cytosolic reduction of iloperidone and back conversion to iloperidone by cytosolic oxidation so that iloperidone

and P88 can be considered to be in equilibrium. There are two major metabolites P88 and P95 with P88 believed to be active.

In the clinical development program the sponsor studied the effect of polymorphisms in the CYP2D6 gene on iloperidone exposure and QT prolongation and in the ciliary neurotrophic factor (CNTF) gene on efficacy. The sponsor presented four clinical studies in which the effect of genetic variation of CYP2D6 and/or CNTF on QT prolongation and iloperidone efficacy was investigated:

- 1) Study CILO522A0104: two-cohort, open-label study. Evaluated PK parameters of iloperidone and its two main metabolites (P88 and P95) in healthy subjects genotyped as CYP2D6 extensive metabolizers (Cohort 1) and poor metabolizers (Cohort 2).
- 2) Study CILO522A2328: pharmacogenetic sub-study conducted to identify CYP2D6 genetic polymorphisms associated with iloperidone exposure and risk for QT prolongation after treatment with iloperidone.
- 3) Study ILP3005: pharmacogenetic sub-study to evaluate the effect of polymorphism in the ciliary neurotrophic factor (CNTF) gene on response to iloperidone
- 4) Study VP-VYV-683-3101: assessed the effect of the *CNTF FS63Ter* mutation on iloperidone efficacy and of CYP2D6 polymorphisms on QTc prolongation.

Iloperidone has a relative bioavailability of approximately 96%. Iloperidone C_{max} occurs at 2 hrs in healthy individuals and it has a half-life of 15-22 hrs. Clearance is decreased by half in poor metabolizers. Half-lives for the metabolites are 25 hrs.

Iloperidone prolongs the QT interval at all three doses studied (i.e., 8 mg b.i.d., 12 mg b.i.d., and 24 mg QD)

There is an approximately 24% increase in exposure in subjects with severe renal failure, but renal is not a major route of excretion thus there was no effect of renal impairment on the excretion of iloperidone.

Characterization of iloperidone pharmacokinetics in subjects with moderate and mild hepatic failure was inconclusive. Excretion of iloperidone in

subjects with mild hepatic disease was confounded and could not be interpreted.

Iloperidone exposure is not increased in the presence of the CYP2D6 substrate dextromethorphan. However, dextromethorphan levels were increased by 15% in the presence of iloperidone.

Ketoconazole inhibits iloperidone's metabolism mediated by CYP450 3A4 resulting in a 50% increase in exposure to iloperidone AUC and Cmax.

Iloperidone mean Cmax values increased to 1.6 in the presence of paroxetine. Simultaneous administration of ketoconazole plus paroxetine resulted in the ratio for least square means for iloperidone increasing to 2.3.

Administration of iloperidone and fluoxetine concomitantly increased exposure to iloperidone and P88 (ratio for AUC0-inf least square means=2.37 and 2.21, respectively), while exposure to P95 had a decrease in the ratio for the least square means (i.e., 0.46 for AUC0-inf). This is a result of blocking the CY2D6 pathway. Iloperidone did not alter the pharmacokinetics of fluoxetine and norfluoxetine.

There is no effect of food on the absorption of iloperidone.

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COMMENTS TO THE MEDICAL OFFICER

A. Hepatic Study

The hepatic impairment study was inconclusive.

The firm will be requested to do a reduced design hepatic impairment study using subjects in the moderate Child-Pugh category.

Pending receipt of the hepatic impairment study data, iloperidone should not be administered to hepatically impaired subjects.

B. Inspection Report

This study was also investigated by the Division of Scientific Investigations. The report concluded that Vanda had included information into their reports without verification which led to some errors, overall it did not impact study outcome. The report is appended to the review.

C. Dissolution Comments

The comments to the sponsor section contains dissolution comments that should be forwarded to the sponsor.

COMMENTS TO THE SPONSOR

1. The study CIL0522A0103 conducted in normal, mild and moderately impaired hepatic subjects was inconclusive since the exposure for mild subjects was greater than for moderately impaired subjects. The sponsor should repeat the study in a moderately impaired group comparing them to normals in the same study. The genotyping for the extensive metabolizers used in this study should be submitted to OCP.
2. The firm should conduct a study investigating the possible in vitro interaction of iloperidone and P-Gp as discussed in a prior communication with the firm.
3. The dissolution method and specification for all strengths of the immediate release tablets should be:
Apparatus 2 (rotating paddle)
500 ml 0.1 N HCl
50 rpm rotation speed.

Q= — in 30 minutes

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QUESTION BASED REVIEW

WHAT IS THE PLASMA PROTEIN BINDING AND RED CELL PARTITIONING FOR ILOPERIDONE AND IS THE PROTEIN BINDING LINEAR?

The plasma protein binding for iloperidone is 93% and it is linear over the range of 5-500 ng/ml.

The fraction of iloperidone in the red blood cells is 25% in the concentration range of 10-100 ng/ml.

WHAT ARE THE MAJOR METABOLITES FOR ILOPERIDONE BASED UPON THE HUMAN LIVER ENZYME STUDIES?

IL0522 was metabolized in human liver microsomes to primarily four products, P22 (N-dealkylation), P94 (hydroxylation), P89 (O-demethylation), and P88 (carbonyl reduction).

CYP2D6 was the most efficient in the formation of metabolite P94 (hydroxylation)

Table 1. Per Cent metabolism of IL0522 by recombinant cytochrome P450's

P450	IL0522 metabolites formed (% of total)	IL0522 metabolites identified in screen
CYP1A1	21	P22, P88
CYP1A2	4.7	P22, P88
CYP2A6	1.2	P88
CYP2B6	3.2	P22, P88
CYP2C8	5.6	P22, P88
CYP2C9	1.8	P22
CYP2C19	7.2	P22, P88, P89
CYP2D6	15	P94
CYP2E1	0.7	P22
CYP3A4	9-15	P22, P88, P89
CYP3A5	4.9	P22, P88, P89

WHAT IS THE MASS BALANCE FOR ILOPERIDONE?

The mass balance for iloperidone was determined following the oral administration of 3 mg of 100 uCi of ¹⁴C-iloperidone to 3 male volunteers.

Table 2. Total radioactivity excreted in urine and feces

	Subject 2 Cumulative % of Dose	Subject 4 Cumulative % of Dose	Subject 5 Cumulative % of Dose	Mean ± SD Cumulative % of Dose
Urine	50.2	64.2	54.5	56.3 ± 7.2
Feces	19.6	19.7	22.5	20.6 ± 1.6
Total % of Radioactivity Recovered	69.8	83.9	77.0	76.9 ± 7.1

Over the 21 day collection period most of the radioactivity was recovered in the urine.

The major urinary component was HU10, which comprised of two components; an aryl carboxylic acid metabolite (P95-12113) and metabolite P88-8991. This component accounted for between 9% and 65% of the urinary radioactivity in the samples analyzed.

The mean total fecal recovery at the end of the study (day 42) was similar in all subjects, ranging from 19.6% in subject 2 to 22.5% in subject 5 (mean 20.6 ± 1.6%).

WHAT ARE THE MAJOR CIRCULATING SPECIES IN PLASMA for EM's and PM's?

A study was done with 3 mg [¹⁴C]ILO522 given as an oral solution to six healthy, nonsmoking, male subjects between the ages of 18 and 45 years.

Pharmacokinetic and safety assessments were made for up to 336 hours (14 days). Four of the subjects were EM's and two were PM's.

Table 3. AUC(0-t) (ngEq*h/ml) values for major species identified in plasma and the amount of total radioactivity associated with that component for two representative EM subjects and the two PM subjects

AUC(0-t) (ngEq*h/ml) of Major Species Measured in Plasma					
	iloperidone	P88	P95	IIO 522 N-dealkyl	Total % Radioactivity Extracted
EM					
EM					
PM					
PM					

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The results indicate that there is a quantitative recovery of species in plasma for EM's and for PM's.

IS THERE A DIFFERENCE IN THE AMOUNT OF DRUG RECOVERY FOR SLOW AND FAST METABOLIZERS?

A drug recovery study was done in 4 extensive and 2 slow metabolizers.

Table 4. Excretion of dose (radioactivity and unlabeled metabolites, % dose) in the six healthy human volunteers (4 EM, 2 PM) in the 14 days following a single oral dose of 3 mg [¹⁴C]ILO522

		CYP2D6 EM					CYP2D6 PM		
subject		5101	6102	5103	5104	Mean ± SD	5105	5106	Mean ± ^a
Radioactivity	Urine					58.2 ± 8.15			15.1 ± 6.69
	Feces					19.9 ± 3.43			22.1 ± 3.38
	Sum					78.1 ± 8.86			37.2 ± 10.1
Unlabeled Metabolites	Urine					12.3 ± 3.33			16.0 ± 2.82
	Feces					0.71 ± 0.42			2.99 ± 0.1
	Sum					13.0 ± 3.73			18.9 ± 2.92
Dose recovery	Total					91.1 ± 9.07			86.2 ± 7.15

^a Mean and range (N=2).

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The recovery appears to be similar for slow and fast metabolizers and for all sampled fluids and for total dose recovery.

HAS THE CLASSIFICATION OF CYP 2D6 EXTENSIVE AND POOR METABOLIZERS BEEN DONE CORRECTLY BY THE FIRM?

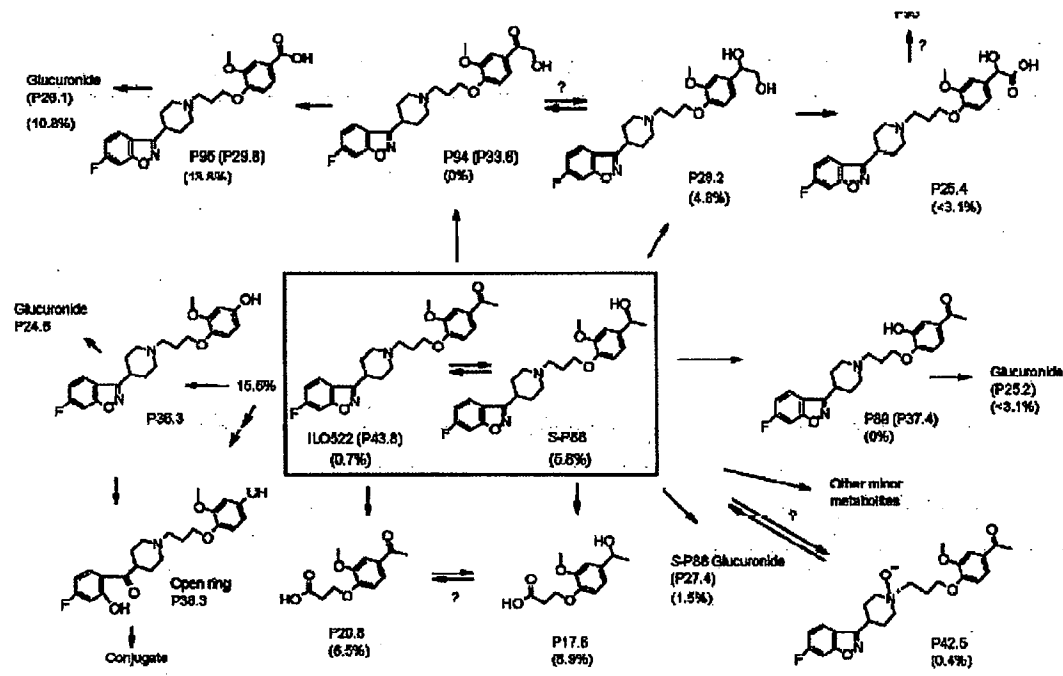
CYP2D6 plays an important role in iloperidone metabolism. It also shows extensive genetic polymorphism, which determines a great variability in the activity of the enzyme in the population. Four phenotypes have been described: poor, intermediate, extensive (regarded as the normal phenotype) and ultrarapid metabolizers. The effect of CYP2D6 status on the PK of drugs metabolized by CYP2D6 is usually evaluated by comparing drug exposure in poor (PM) and extensive metabolizers (EM). The identification of PM and EM (also called CYP2D6*1/*1) wild type can be done by genotyping for the most common CYP2D6 alleles in the studied population (those alleles are different in different ethnic groups). However, there is no specific test to identify the *1 allele and its presence is defined by the absence of the tested alleles. Therefore, the accuracy of the *1 allele designation depends highly on the number of tested variants. In the case of testing only for one allele (*4), as is the case of the studies presented by the sponsor, assigning the *1/*1 genotype (EM) to those patients that tested negative for *4 could lead to the misclassification of about 30% of the patients. This means that those so-defined "*1/*1" patients could actually be for instance *3/*5 (then PM), *10/*10 (then intermediate) or *1/*2xn (then ultrarapid metabolizers).

WHAT IS THE IMPACT OF THIS LACK OF CLASSIFICATION ON THE ABILITY TO CORRECTLY PREDICT THE EFFECT OF PM IN THE POPULATION AND THE NEED FOR DOSE ADJUSTMENT?

Although CYP2D6*4 is the most frequent knockout allele in Caucasians, that is not the case for other ethnicities, and other alleles such as CYP2D6*3 and *5 can account for up to 30% of the PMs, even in Caucasians. In addition, as stated before, the number of tested alleles affects the identification of the EM as well. If the PM and EM groups are not clearly defined, the validity of any comparison of variables between these groups is questionable.

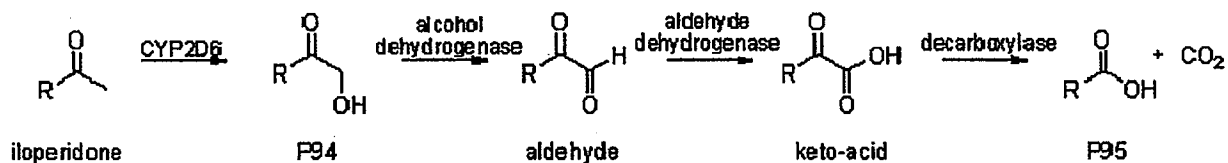
WHAT IS THE PROPOSED METABOLIC SCHEME FOR ILOPERIDONE?

Figure 2. Structures of ILO522 metabolites formed in human in vivo. Numbers in parentheses represent the average amount (% dose) of metabolite(s) in excreta from all six human subjects following a single oral dose of 3 mg ¹⁴C ILO522



Iloperidone is metabolized through multiple pathways, but primarily through CYP2D6, CYP3A4 and cytosolic reduction. P88 is generated from iloperidone by cytosolic reduction, a reaction that is in equilibrium causing the interconversion of iloperidone to P88 and *vice versa*. P88 is primarily eliminated by glucouronidation.

Proposed pathway for conversion of P94 to P95 (carboxylic acid).



P95 is eliminated by glucuronidation.

ARE THE PHARMACOKINETICS FOR ILOPERIDONE AND ITS TWO MAJOR METABOLITES LINEAR?

A 32 patient study was done to investigate the linearity of doses from 2-12 mg bid at steady-state in schizophrenic patients.

Table 5. Estimates and 90% CI for exponent parameters of power model for assessing dose proportionality.

	Parameter	Estimate*	90% Confidence Interval	p-value**
Iloperidone	AUC _t	1.116	(1.06, 1.17)	0.001
	C _{max} ^{ss}	1.148	(1.06, 1.24)	0.009
	C _{min} ^{ss}	1.155	(1.10, 1.21)	<0.001
P88-8991	AUC _t	0.998	(0.97, 1.03)	0.910
	C _{max} ^{ss}	1.002	(0.97, 1.03)	0.928
	C _{min} ^{ss}	0.973	(0.93, 1.02)	0.302
P95-12113	AUC _t	1.025	(0.97, 1.08)	0.463
	C _{max} ^{ss}	1.024	(0.96, 1.08)	0.498
	C _{min} ^{ss}	1.064	0.98, 1.15)	0.227

*The 90% confidence interval for exponent from the analysis of logarithmically transformed data.

**The p-value is from testing for the exponent parameter value equal to 1.

The results indicate that Iloperidone showed some non-linearity over the dosage range of 2-12 mg bid while the major metabolites all exhibited linear pharmacokinetics.

IS THE RENAL EXCRETION OF ILOPERIDONE AFFECTED BY RENAL FAILURE?

The firm conducted a study in two groups:

Group 1: Subjects between 18 and 65 years of age with chronic, severe renal failure (CrCL <30 mL/min).

Group 2: Healthy male and non-fecund female subjects matched by gender, age, height, body weight, and smoking status to Group 1 (CrCL >80 mL/min).

A total of 23 subjects completed the study, with 3 additional healthy subjects requiring dosing due to study site mismatching subjects (Subjects 14, 15, & 18). No subject discontinued from the study.

A single 3-mg dose (3 x 1-mg capsules) was administered.

RESULTS

Figure 3. Mean plots of iloperidone in healthy and renally impaired subjects following a 3 mg oral dose.

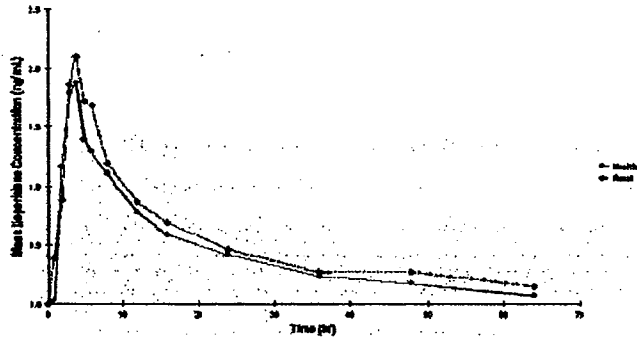


Table 6. Mean %CV parameters of iloperidone in healthy and renally impaired subjects following a 3 mg oral dose

PK Parameters	Mean (CV%)		
	Healthy Subjects	Renally Impaired Subjects	% Difference
t_{max} (hr)*	3.0 (2-5)	4.0 (3-4)	-
C_{max} (ng/mL)	2.2 (35)	2.3 (71)	5
AUC_{0-4} (ng·hr/mL)	27.8 (38)	34.5 (85)	24
$t_{1/2}$ (hr)	15.0 (20)	33.7 (48)	124
CL_T/F (L/hr)	120.2 (32)	97.3 (59)	-19
V_d/F (L)	2527 (23)	4049 (45)	60
Ae (mcg)	17.7 (101)	--	-

*Median (range)

Figure 4: Mean concentration-time profiles of metabolite P88-8991 in healthy and renally impaired subjects following 3-mg single oral dose of iloperidone.

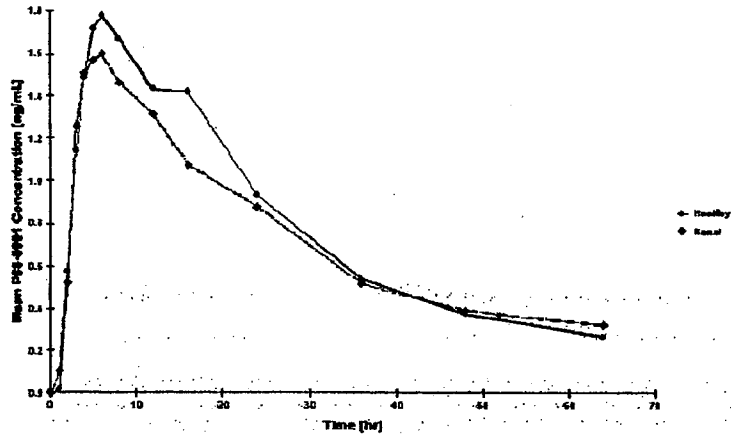


Table 7. Mean (CV%) of pharmacokinetic parameters of P88-8991 in healthy and renally impaired subjects following a 3-mg single oral dose of iloperidone (Subjects 9, 14, 15, 18, and 19 excluded)

PK Parameters	Mean (CV%)		
	Healthy Subjects	Renally Impaired Subjects	% Difference
t_{max} (hr) ^a	6.0 (3-16)	6.0 (3-12)	-
C_{max} (ng/mL)	2.1 (38)	2.0 (40)	-5
AUC_{0-4} (ng·hr/mL)	51.1 (53)	48.1 (49)	-6
$t_{1/2}$ (hr)	25.6 (15)	22.8 (27)	-11
Ae (mcg)	142.9 (64)	--	-

^aMedian (range)

Figure 5: Mean concentration-time profiles of metabolite P95 in healthy and renally impaired subjects following 3-mg single oral dose of iloperidone.

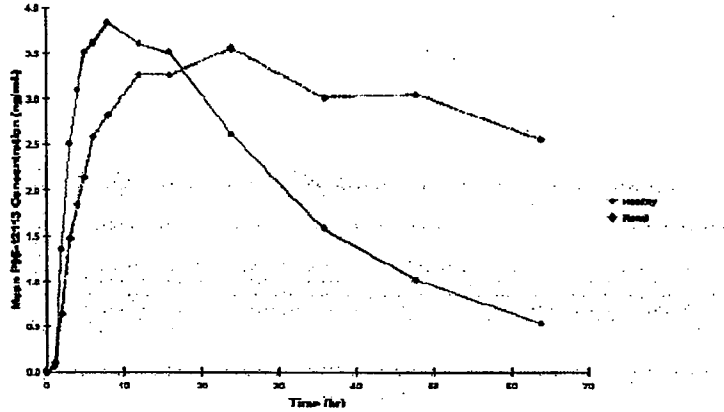


Table 8. Mean (CV%) of pharmacokinetic parameters of P95-12113 in healthy and renally impaired subjects following 3-mg single oral dose of iloperidone (Subjects 9, 14, 15, 18, and 19 excluded)

PK Parameters	Mean (CV%)		
	Healthy Subjects	Renally Impaired Subjects	% Difference
t_{max} (hr)	8 (5-24)	24 (8-24)	-
C_{max} (ng/mL)	4.2 (58)	3.9 (54)	-7
$AUC_{0-\infty}$ (ng·hr/mL)	126.1 (50)	192.3 (63)	52
$t_{1/2}$ (hr)	19.3 (20)	82.8 (34)	329
Ae (mcg)	277.4 (50)	--	--

The 24% increase in exposure for iloperidone in this study does not warrant any change in dose for renally impaired subjects.

For the active metabolite P88 there was also no effect of renal impairment on total or peak exposure.

The inactive metabolite P95 had a 52% increase in total exposure for renally impaired subjects whereas there was no effect of renal impairment on peak concentration.

WHAT IS THE EFFECT OF MILD AND MODERATE HEPATIC FAILURE ON THE METABOLISM OF ILOPERIDONE?

Study Group 1 consisted of 4 subjects with mild hepatic impairment (Child-Pugh Score 5-6; 2 males, 2 females) and 4 subjects with moderate hepatic impairment (Child-Pugh Score 7-9; 4 males). Group 2 consisted of 8 healthy subjects matched by gender, age, body height, weight, and smoking status (4 subjects in each group) to Group 1.

All subjects were extensive metabolizers.

Figure 6. Mean plots of iloperidone in healthy and hepatically impaired subjects by severity following a 2-mg single oral dose of iloperidone

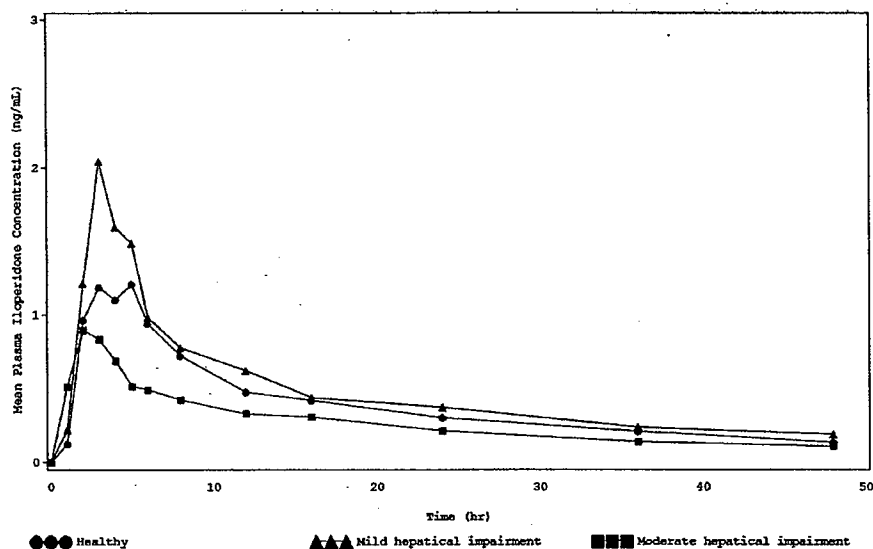
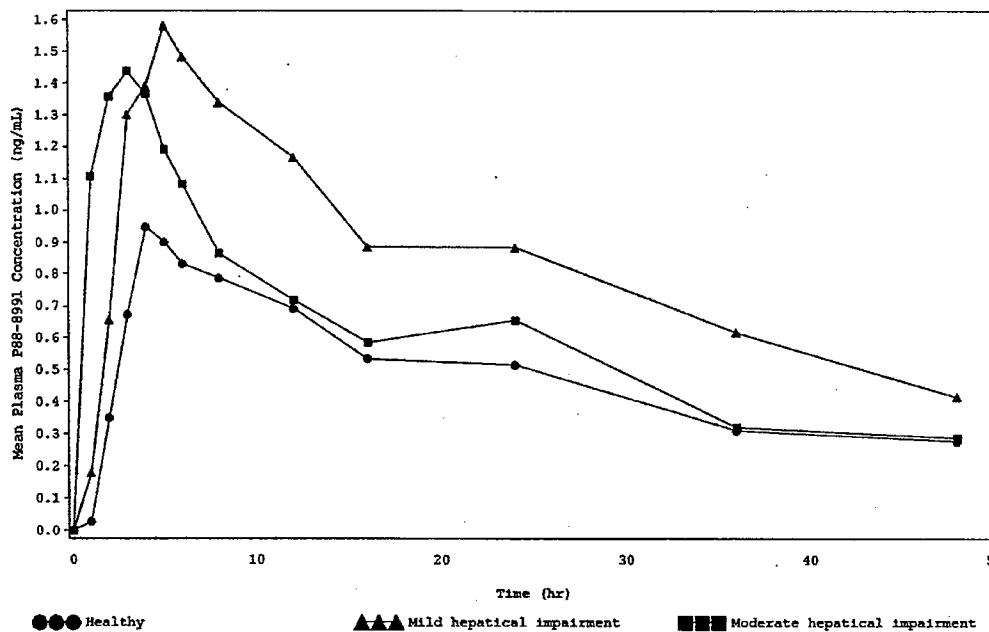


Table 9. Mean (cv%) pharmacokinetic parameters for iloperidone in healthy and hepatically impaired subjects by severity following a 2 mg oral dose of iloperidone.

PK Parameters	Mean (CV%)				
	Healthy Subjects (N=8)	Hepatically Impaired Subjects (N=4)		Hepatically Impaired Subjects (N=4)	
			Mild	% Difference	Moderate
t_{max} (hr)	3.50 (2-5)	3.50 (3-5)	0.0	1.75 (1-3)	-50.0
C_{max} (ng/mL)	1.75 (56.2)	2.23 (15.4)	27.2	1.13 (35.4)	-35.4
AUC_{0-4} (ng*hr/mL)	18.78 (40.0)	23.60 (17.7)	25.7	12.79 (67.0)	-31.9
$AUC_{0-\infty}$ (ng*hr/mL)	22.00 (36.3)	30.33 (20.2)	37.8	20.77 (61.7)	-5.6
$t_{1/2}$ (hr)	24.44 (29.9)	24.45 (14.3)	0.0	24.57 (26.7)	0.5
Cl_r/f_m (L/hr)	102.71 (34.3)	68.25 (23.2)	-32.5	122.07 (52.5)	18.8
V_d/f_m (L)	3702.29 (52.9)	2394.25 (24.4)	-35.3	2955.33 (36.2)	6.8
λ_e (% of dose)	0.40 (69.9)	0.44 (56.2)	9.8	0.34 (58.5)	-15.8
Cl_e (mL/min)	7.02 (44.3)	6.46 (82.5)	-7.7	13.05 (86.2)	85.9

Figure 7. Mean plots of P88-8991 in healthy and hepatically impaired subjects by severity following a 2-mg single oral dose of iloperidone.



Results were confounded and the firm will be requested to repeat the study using the modified design.

Label should reflect the fact that a study has not been done for Iloperidone during hepatic impairment and that it should not be given to subjects with mild, moderate and severe hepatic impairment. The reasons for this decision are:

1. the hepatic study was done at one of the lowest doses which could pose a more significant safety issue at higher doses.
2. the pattern presented by the data has mild subjects exhibiting exposures approximately 50% higher than moderately impaired subjects for iloperidone.
3. the active metabolite, P88, also appears to exhibit greater exposure for mild than moderately impaired hepatic subjects.

WHAT IS THE EFFECT OF FAST AND SLOW METABOLISM ON THE DISPOSITION OF ILOPERIDONE?

Nineteen subjects were genotyped as extensive CYP2D6 metabolizers and eight subjects were genotyped as poor CYP2D6 metabolizers. All subjects were between the ages of 18 and 45 years. The study objective was to compare the elimination pattern of iloperidone and its metabolites in EM's and PM's.

Figure 8. Mean plots of iloperidone in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

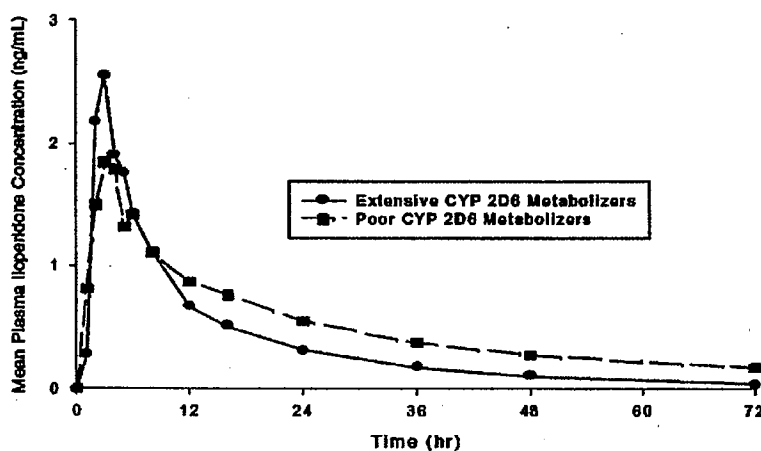


Table 10. Mean (CV%) iloperidone pharmacokinetic parameters in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

PK Parameters	Mean (CV%)		
	Extensive	Poor	% Difference**
T _{max} (hr) [*]	2.5 (2-3)	3 (1-4)	–
C _{max} (ng/mL)	2.79 (27)	2.26 (13)	-19.0
AUC _{0-∞} (ng*hr/mL)	29.4 (36)	46.3 (17)	57.4
t _{1/2} (hr)	17.6 (36)	32.8 (21)	88.3
CL _{T/F} (L/hr)	116.5 (39)	66.4 (16)	-43.0
V _{Z/F} (L)	2868 (49)	3095 (19)	7.9
Ae (% of dose)	0.45 (69)	0.70 (34)	35.7
CL _R (mL/min)	8.2 (56)	9.28 (25)	13.1
[*] Median (Range)			
^{**} % Difference = (Poor – Extensive)/Extensive X 100			

Figure 9. Mean plots of metabolite P88-8991 in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

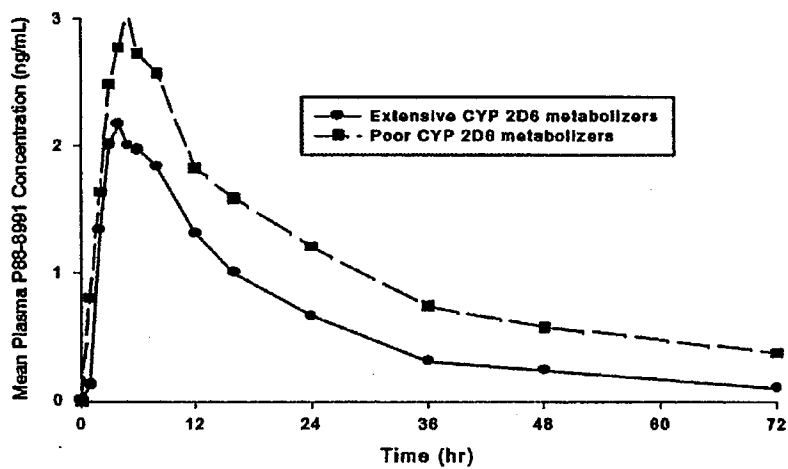


Table 11. Mean (CV%) P88-8991 pharmacokinetic parameters in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of lloperidone

PK Parameters	Mean (CV%)		
	Extensive	Poor	% Difference**
T_{max} (hr)	4.0 (3-6)	4.5 (3-6)	—
C_{max} (ng/mL)	2.32 (30)	3.33 (20)	43.5
$AUC_{0-\infty}$ (ng*hr/mL)	49.4 (43)	96.4 (21)	95.1
$t_{1/2}$ (hr)	25.5 (45)	37.3 (20)	46.3
$CL_T/f_m \cdot F$ (L/hr)	68.7 (32)	32.3 (20)	-53.0
$V_z/f_m \cdot F$ (L)	2343 (45)	1715 (21)	-26.8
A_e (% of dose)	4.2 (57)	8.0 (30)	90.5
CL_R (mL/min)	46.5 (35)	51.3 (16)	10.3
Median (Range)			
** % Difference = (Poor - Extensive)/Extensive X 100			

Figure 10. Mean plots of metabolite P95-12113 in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of lloperidone

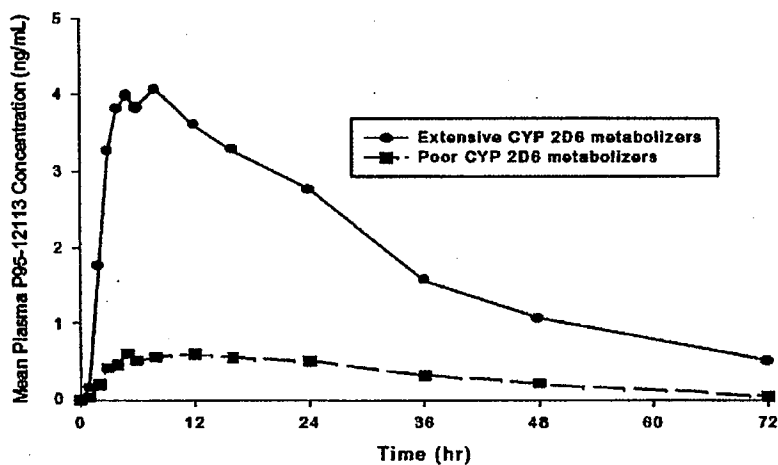


Table 12. Mean (CV%) P95-12113 pharmacokinetic parameters in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone.

PK Parameters	Mean (CV%)		
	Extensive	Poor	% Difference**
T _{max} (hr) [*]	6.0 (3-16)	8.0 (3-12)	–
C _{max} (ng/mL)	4.5 (34)	0.67 (44)	-85.0
AUC _{0-∞} (ng*hr/mL)	153.8 (26)	32.1 (36)	-79.1
t _{1/2} (hr)	23.0 (20)	30.6 (31)	33.0
CL _T /f _m *F (L/hr)	21.5 (41)	101.4 (26)	380.9
V _Z /f _m *F (L)	730.3 (53)	4520 (53)	519.1
Ae (% of dose)	19.2 (31)	4.5 (24)	-76.5
CL _R (mL/min)	66.4 (26)	75.0 (25)	12.9
[*] Median (Range)			
^{**} % Difference = (Poor – Extensive)/Extensive X 100			

Table 13. Least-squares mean ratio of PK parameters from ANOVA of poor vs. extensive metabolizers

	Parameter	Least-squares mean ratio [†]	90% confidence interval [†]
Iloperidone	AUC ₀₋₈	1.659	(1.306,2.107)
	AUC _{0-t}	1.474	(1.161,1.871)
	C _{max}	0.860	(0.691,1.069)
	? C _{max}	0.807	(0.695,0.938)
	CL _R	1.280	(0.878,1.867)
	‡ CL _T /F	0.603	(0.475,0.765)
	Ae _{0-t}	1.599	(1.067,2.396)
P88-8991	AUC ₀₋₈	2.052	(1.621,2.596)
	AUC _{0-t}	1.85	(1.482,2.308)
	C _{max}	1.476	(1.203,1.811)
	CL _R	1.166	(0.906,1.501)
	Ae _{0-t}	1.933	(1.426,2.619)
P95-12113	AUC ₀₋₈	0.208	(0.165,0.261)
	* AUC _{0-t}	0.145	(0.104,0.202)
	C _{max}	0.147	(0.105,0.204)
	CL _R	1.131	(0.940,1.361)
	* Ae _{0-t}	0.197	(0.148,0.261)

Conclusions based on LSM ratios:

1. iloperidone exposure (AUC_{0-t}) was 47% higher for PM's compared to EM's
2. active metabolite exposure was 85% higher for PM's compared to EM's
3. the P95 metabolite exposure was 85% lower for PM's compared to EM's

WAS THERE AN OBSERVED QT PROLONGATION?

The firm conducted an open-label study comparing iloperidone at doses of 8 mg b.i.d., 12 mg b.i.d., and 24 mg q.d. on QTc interval duration in the presence and absence of metabolic inhibition. The effect of metabolic inhibition on iloperidone and the active comparators (ziprasidone 80 mg b.i.d, and quetiapine 375 mg b.i.d., in the presence and absence of metabolic inhibition), in otherwise healthy patients diagnosed with schizophrenia or schizoaffective disorder was investigated.

Table 14. Study Design (Treatment phase)

Phase	Treatment phase		
Period	Treatment Period 1	Treatment Period 2	Treatment Period 3
Iloperidone 8 mg b.i.d.	Days 1-15	Days 16 – 23 (+paroxetine)	Days 24 – 28 (+paroxetine and ketoconazole)
Iloperidone 12 mg b.i.d.	Days 1-17	Days 18 –25 (+paroxetine)	Days 26 –30 (+paroxetine and ketoconazole)
Iloperidone 24 mg q.d.	Days 1-18	Days 19 –26 (+paroxetine)	Days 27 –31 (+paroxetine and ketoconazole)
Risperidone 4 mg b.i.d.	Days 1-13	Days 14 – 21 (+paroxetine)	-
Ziprasidone 80 mg b.i.d.	Days 1-10	Days 11 – 15 (+ketoconazole)	-
Quetiapine 375 mg b.i.d.	Days 1-12	Days 13 – 17 (+ketoconazole)	-

Table 15. Summary statistics of QTcF change (95% CI) from baseline to steady state at Tmax during Treatment Periods 1, 2, and 3 (Primary QTc population).

	Ilo 8 mg	Ilo 12 mg	Ilo 24 mg	Zip	Quet
Period 1					
<i>Sample size</i>	28	34	31	32	33
<i>Baseline</i>					
Raw mean $\pm$ SD	385.9 $\pm$ 16.4	386.5 $\pm$ 17.1	379.0 $\pm$ 14.7	383.4 $\pm$ 13.5	383.2 $\pm$ 18.9
<i>Change in QTcF</i>					
Raw mean $\pm$ SD	8.5 $\pm$ 10.5	9.0 $\pm$ 12.5	15.4 $\pm$ 11.7	9.6 $\pm$ 11.0	1.3 $\pm$ 11.1
LS mean*	9.1	9.7	14.6	9.7	1.3
(95% CI for LS mean)	(4.9, 13.3)	(5.8, 13.6)	(10.6, 18.9)	(5.7, 13.7)	(-2.5, 5.2)
Period 2					
<i>Sample size</i>	26	31	31	30	32
<i>Baseline</i>					
Raw mean $\pm$ SD	387.3 $\pm$ 16.1	386.1 $\pm$ 17.7	379.0 $\pm$ 14.7	383.0 $\pm$ 13.2	382.8 $\pm$ 19.1
<i>Change in QTcF</i>					
Raw mean $\pm$ SD	11.2 $\pm$ 12.0	11.6 $\pm$ 16.8	17.5 $\pm$ 10.3	15.9 $\pm$ 11.8	2.6 $\pm$ 11.5
LS mean	11.9	11.9	16.0	15.4	2.1
(95% CI for LS mean)	(7.2, 16.6)	(7.6, 16.3)	(11.7, 20.3)	(11.1, 19.8)	(-2.1, 6.3)
Period 3					
<i>Sample size</i>	25	30	29	—	—
<i>Baseline</i>				—	—
Raw mean $\pm$ SD	387.5 $\pm$ 16.4	384.5 $\pm$ 15.6	379.6 $\pm$ 14.9	—	—
<i>Change in QTcF</i>				—	—
Raw mean $\pm$ SD	15.7 $\pm$ 14.1	19.3 $\pm$ 17.1	19.5 $\pm$ 11.9	—	—
LS mean	15.8	18.5	17.6	—	—
(95% CI for LS mean)	(10.1, 21.6)	(13.2, 23.9)	(12.3, 22.9)	—	—

* The least square means and confidence intervals for Period 1 are provided by the reviewer. These results are slightly different than the results reported on Table 9.2.1-2, page 308 as the sponsor's results included two additional patients from the secondary QTc population)

The results indicated that the 95% 1-sided CI contained 10 msec at the doses of 8 mg, 12 mg and 24 mg.

WERE THERE ANY DESIGN ISSUES RELATED TO THE QT DATA PRESENTED THAT WOULD LIMIT THE PRECISE ESTIMATION OF THE EFFECT?

The major limitations were as follows:

1. This study was not a placebo-controlled study. There were two active controls, ziprasidone 80 mg b.i.d. and quetiapine 375 mg b.i.d., but the magnitude of their effects on the QT interval is not well characterized.
2. All treatments were administered open-label. Thus, the study is subject to potential bias.

3. Assay sensitivity could not be established. The study included two active comparators: quetiapine (375 mg b.i.d.) and ziprasidone (80 mg b.i.d.). Based on the FDA analysis of the exposure-response analysis for quetiapine in two other QT studies (Study A750-1001 in NDA 22,192 and Study R076477-SCH-1014 in NDA 21,999), it is expected that quetiapine will increase the QT interval in a concentration-dependent manner, with an approximate effect size of 7-10 ms for a mean C_{max} of 1,000 to 1,200 ng/ml quetiapine. In this study, quetiapine did not prolong the QT interval despite achieving mean steady-state peak concentration of 826 ng/ml. Therefore, the confidence in the estimated effect size of administering iloperidone on QTc is low.

WHAT IS THE EFFECT OF THE INTERACTION OF ILOPERIDONE AND DEXTROMETHOPHAN (i.e., a CYP2D6 substrate) ON THE CYP2D6 ENZYME?

A study was done in 19 subjects, between the ages of 18 and 45 years, genotyped as extensive CYP2D6 metabolizers and eight subjects were genotyped as poor CYP2D6 metabolizers.

Table 16. Treatment Design

	Period 1	Period 2	Period 3
Cohort 1/Sequence 1	iloperidone	dextromethorphan + iloperidone	dextromethorphan
Cohort 1/Sequence 2	iloperidone	dextromethorphan	dextromethorphan + iloperidone
Cohort 2/Sequence 1	iloperidone		

Subjects received a single dose of 3 mg iloperidone in Period 1; in Period 2 and 3 subjects received 80 mg dextromethorphan and 3 mg iloperidone + 80 mg dextromethorphan in random order.

EFFECT OF DEXTROMETHORPHAN ON ILOPERIDONE

Table 17. Least-squares mean ratio of PK parameters (AUC₀₋₈, AUC_{0-t}, C_{max}, and CL_{T/F}) from ANOVA of iloperidone + dextromethorphan vs. iloperidone alone.

	Parameter	Least-squares mean ratio *	90% confidence interval *
Iloperidone	AUC ₀₋₈	1.013	(0.958,1.071)
	AUC _{0-t}	1.015	(0.962,1.071)
	C _{max}	1.006	(0.911,1.112)
	CL _R	1.198	(0.972,1.478)
	‡ CL _{T/F}	0.987	(0.935,1.043)
	Ae _{0-t}	1.133	(0.940,1.366)
P88-8991	AUC ₀₋₈	1.025	(0.968,1.085)
	AUC _{0-t}	1.013	(0.955,1.073)
	C _{max}	1.058	(0.985,1.132)
	* CL _R	1.151	(0.993,1.335)
	Ae _{0-t}	1.119	(0.976,1.284)
P95-12113	AUC ₀₋₈	1.005	(0.961,1.050)
	AUC _{0-t}	0.987	(0.939,1.037)
	C _{max}	1.015	(0.960,1.073)
	CL _R	1.044	(0.969,1.124)
	Ae _{0-t}	1.030	(0.965,1.099)

Conclusion:

Based upon ratio of Least Square Means

1. dextromethorphan has no effect on iloperidone exposure
2. dextromethorphan has no effect on P88 exposure
3. dextromethorphan has no effect on P95 exposure

EFFECT OF ILOPERIDONE ON DEXTROMETHORPHAN

Table 18. Least-squares mean ratio of PK parameters (AUC₀₋₈, AUC_{0-t}, C_{max}, and CL_T/F) from ANOVA of iloperidone + dextromethorphan vs. dextromethorphan alone

	Parameter	Least-squares mean ratio *	90% confidence interval *
Dextromethorphan	AUC ₀₋₈	1.123	(1.008,1.251)
	AUC _{0-t}	1.171	(1.045,1.311)
	C _{max}	1.264	(1.053,1.517)
	‡ CL _T /F	0.891	(0.800,0.992)
Dextrophan	AUC ₀₋₈	1.007	(0.980,1.034)
	AUC _{0-t}	1.027	(0.995,1.060)
	* C _{max}	0.945	(0.910,0.980)

Conclusion:

Based upon ratio of Least Square Means

1. dextromethorphan AUC (0-t) ratio increased to 1.17.
2. dextromethorphan C_{max} ratio increased to 1.26.
3. dextrophan exposure was not altered by the presence of iloperidone.

WHAT IS THE EFFECT OF KETOCONAZOLE ON THE PLASMA LEVELS OF ILOPERIDONE AND ITS METABOLITES?

A 19 subject two-period, open-label, randomized, cross-over study design with a 21-day screening period study was done to investigate the effect of ketoconazole on Iloperidone metabolism. There were 2 study sequences:

Sequence 1

Subjects dosed with 200 mg ketoconazole twice daily for 4 days and iloperidone was administered as a 3 mg single dose after the 7th dose of ketoconazole.

Sequence 2

1. Iloperidone was given alone in Period 1, 3 mg, and iloperidone and ketoconazole combination in Period 2.

A 14-day washout interval (approximately 12 days outpatient) separated iloperidone single doses.

Figure 11. Mean plots of iloperidone following 3 mg single oral dose of iloperidone administered alone (A) or in combination with multiple doses of ketoconazole (B)

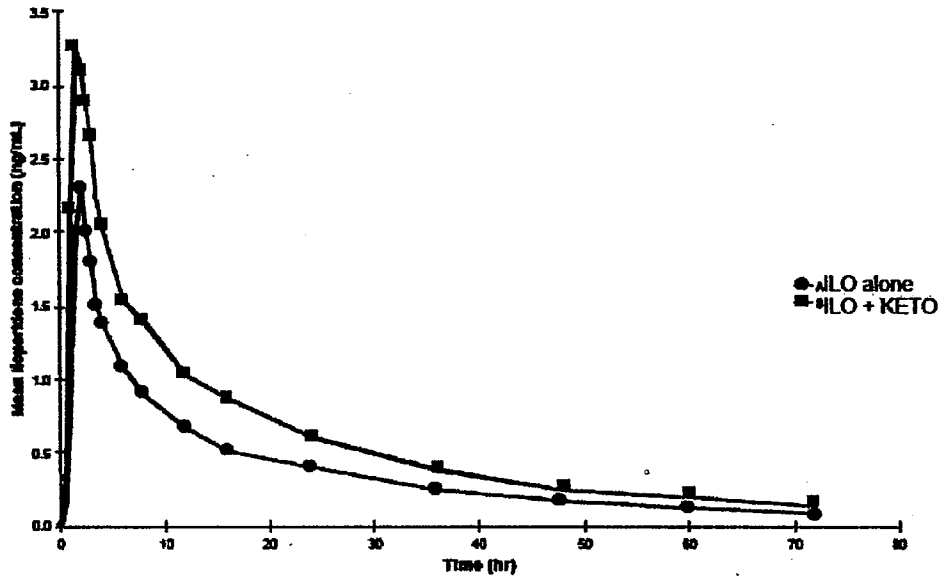


Table 20. Mean (CV%) pharmacokinetic parameters of iloperidone following 3 mg single oral dose of iloperidone administered alone or in combination with multiple doses of ketoconazole

Parameters	Mean (CV%)		% Difference**
	Ilo alone	Ilo with keto	
t_{max} (hr)	2.0 (1-3)	1.8 (1-3)	-
C_{max} (ng/mL)	2.64 (48)	3.72 (26)	48
AUC_{0-1} (ng·hr/mL)	28.6 (47)	44.3 (37)	56
AUC_{0-72} (ng·hr/mL)	32.6 (47)	48.7 (43)	53
$t_{1/2}$ (hr)	28.3 (28)	26.6 (19)	-2
$CL_{1/2}$ (L/hr)	110.7 (48)	88.1 (33)	-38
V _d /F (L)	4084 (45)	2684 (48)	-57
A_e (% of dose)	0.227 (86)	0.301 (78)	33
CL_R (mL/min)	4.24 (88)	3.48 (63)	-18

Figure 12. Mean plots of P88-8991 following 3 mg single oral dose of iloperidone administered alone (A) or in combination with multiple doses of ketoconazole (B)

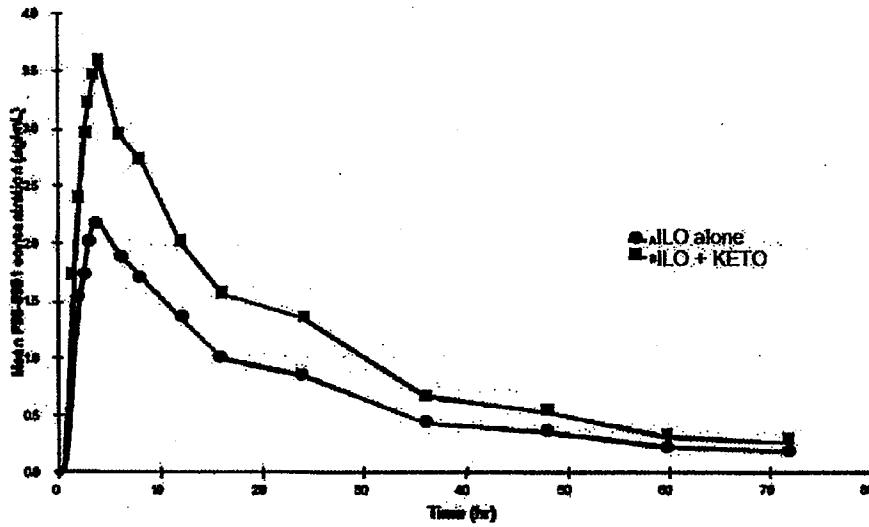


Table 21. Mean (CV%) pharmacokinetic parameters of P88-8991 following 3 mg single oral dose of iloperidone administered alone or in combination with multiple doses of ketoconazole

Parameters	Mean (CV%)		% Difference**
	Ilo alone	Ilo with keto	
t_{max} (hr)	4.0 (3.8)	4.0 (3.8)	--
C_{max} (ng/mL)	2.31 (38)	3.88 (23)	68
AUC_{0-8} (ng-h/mL)	49.0 (36)	78.2 (28)	58
$AUC_{0-\infty}$ (ng-h/mL)	57.1 (38)	86.9 (28)	60
$t_{1/2}$ (hr)	28.1 (20)	28.1 (19)	0
$CL_{1/2}F$ (L/hr)	80.7 (41)	38.2 (32)	-37
V_d/F (L)	2188 (36)	1318 (29)	-40
A_e (% of dose)	2.88 (63)	3.75 (64)	30
CL_R (mL/min)	29.8 (38)	24.1 (41)	-19
*Median (Range)			
** % Difference = (Ilo with Keto - Ilo alone)/Ilo alone X 100			

Figure 13. Mean plots of P95-12113 following 3 mg single oral dose of iloperidone administered (A) alone or in combination with multiple doses of ketoconazole (B)

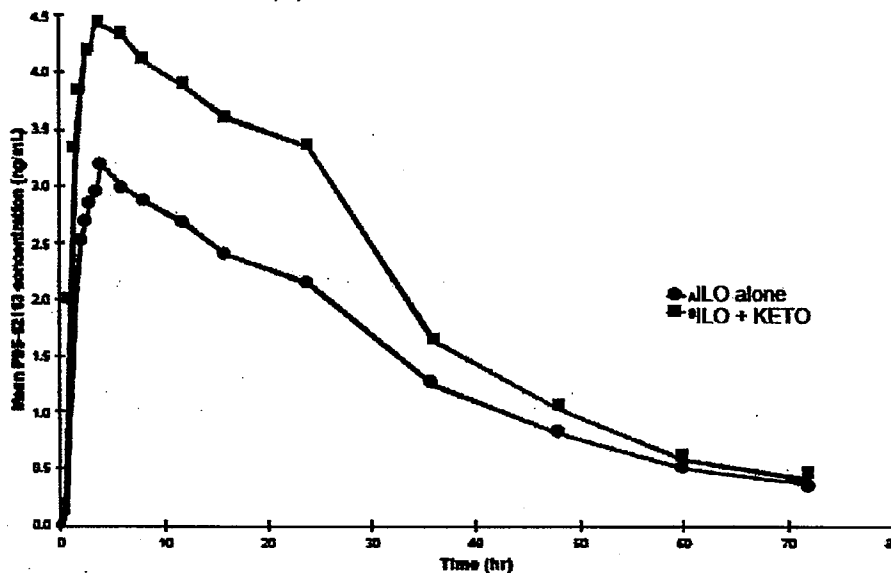


Table 22. Mean (CV%) pharmacokinetic parameters of P95-12113 following 3 mg single oral dose of iloperidone administered alone or in combination with multiple doses of ketoconazole

Parameters	Mean (CV%)		% Difference**
	Ilo alone	Ilo with keto	
t_{max} (hr)	4.0 (3-18)	6.0 (2-24)	--
C_{max} (ng/mL)	3.39 (48)	4.87 (54)	42
$AUC_{0-\infty}$ (ng·hr/mL)	104.6 (40)	149.6 (48)	43
AUC_{0-72} (ng·hr/mL)	118.0 (38)	160.4 (44)	38
$t_{1/2}$ (hr)	20.3 (20)	18.9 (32)	-7
$CL_{1/2,0-72}$ (L/hr)	33.7 (79)	24.8 (71)	-28
V_d/F_{po} (L)	1020 (44)	789.3 (130)	-22
A_e (% of dose)	8.91 (38)	11.6 (42)	17
CL_e (mL/min)	52.6 (42)	42.4 (44)	-19

*Median (Range)
 ** % Difference = (Ilo with Keto - Ilo alone)/Ilo alone X 100

Table 23. Least-squares mean ratio of pharmacokinetic parameters from ANOVA of iloperidone + ketoconazole vs. iloperidone alone

	Parameter	Least-squares mean ratio *	90% confidence interval *
iloperidone	AUC _{0-t}	1.61	(1.51, 1.71)
	AUC _{0-∞}	1.57	(1.48, 1.66)
	C _{max}	1.55	(1.39, 1.72)
	CL _r /F	0.64	(0.68, 0.60)
	CL _R	0.83	(0.68, 1.00)
	A _s	1.33	(1.10, 1.59)
P88-8991	AUC _{0-t}	1.60	(1.49, 1.72)
	AUC _{0-∞}	1.55	(1.44, 1.66)
	C _{max}	1.63	(1.49, 1.79)
	CL _r	0.80	(0.69, 0.93)
	A _s	1.31	(1.16, 1.48)
	P95-12113	AUC _{0-t}	1.39
AUC _{0-∞}		1.35	(1.25, 1.43)
C _{max}		1.35	(1.26, 1.45)
CL _r		0.78	(0.71, 0.86)
A _s		1.09	(0.98, 1.21)

*: The ratio of least-squares means and the 90% confidence interval were obtained from the analysis of logarithmically transformed data.

‡: Since $CL/F = \text{dose}/AUC_{0-\infty}$, the least-squares mean of CL/F and its 90% confidence limits were obtained by taking the reciprocals of those of $AUC_{0-\infty}$.

Conclusions:

Based upon ratio of Least Square Means :

1. Co-administration of multiple doses of ketoconazole 200 mg and a single dose of iloperidone 3 mg resulted in approximately 50% increase in exposure to iloperidone AUC and C_{max}. Thus, ketoconazole inhibits iloperidone's metabolism mediated by CYP450 3A4.

2. This inhibition and consequent increase in iloperidone exposure led to an increase in exposure to the two metabolites, P88-8991 and P95-12113, by 55 and 35 % respectively.

WHAT IS THE EFFECT OF FLUOXETINE CYP 2D6 INHIBITOR ON THE METABOLISM OF ILOPERIDONE?

An 18 subject open-label, 3-period, 1-sequence crossover study design study was done to investigate the following treatments:

1. Treatment A – iloperidone 3mg single dose

2. Treatment B-multiple dose of fluoxetine 20 mg bid
3. Treatment C-multiple dose fluoxetine 20 mg bid + iloperidone 3 mg

Dosing days were:

Treatment A -Day 1

Treatment B -Days 8-28

Treatment C -Day 29

Samples were taken on days 1 and 29 to measure iloperidone and on days 28 and 29 to measure fluoxetine.

All subjects received both treatments in the same sequence.

FLUOXETINE ON ILOPERIDONE

Table 24. Least-squares mean ratio and 90% confidence intervals for pharmacokinetic parameters of iloperidone and its metabolites from ANOVA for iloperidone with fluoxetine vs iloperidone alone

	Parameter	Least-squares mean ratio ^a	90% confidence interval ^a
Iloperidone	AUC _{0-∞}	2.37	(2.05,2.73)
	AUC _{0-t}	2.24	(1.94,2.58)
	C _{max}	1.68	(1.48,1.92)
	t _{1/2}	1.37	(1.19,1.58)
P88-8991	AUC _{0-∞}	2.21	(1.94,2.52)
	AUC _{0-t}	2.16	(1.91,2.44)
	C _{max}	1.65	(1.47,1.85)
	t _{1/2}	1.31	(1.14,1.51)
P95-12113	AUC _{0-∞}	0.469	(0.384,0.572)
	AUC _{0-t}	0.358	(0.297,0.431)
	C _{max}	0.313	(0.262,0.374)
	t _{1/2}	1.25	(1.11,1.42)

^a The ratio of least-squares means of iloperidone with fluoxetine vs. iloperidone and the 90% confidence interval were obtained from the analysis of logarithmically transformed data.

Conclusions:

Based upon ratio of Least Square Means :

1. Exposure to iloperidone and P88-8991 was significantly increased 137% and 121% respectively for AUC_{inf} while exposure to P95-12113 was significantly decreased by 53% following concomitant administration of iloperidone and fluoxetine as compared to iloperidone alone.

ILOPERIDONE ON FLUOXETINE

Table 25. Least-squares mean ratio and 90% confidence intervals for pharmacokinetic parameters of fluoxetine and its metabolite from ANOVA for iloperidone with fluoxetine vs fluoxetine alone

	Parameter	Least-squares mean ratio ^a	90% confidence interval ^a
Fluoxetine	AUC ₀₋₁₂	1.03	(0.991,1.06)
	C _{max} ^{ss}	1.01	(0.978,1.05)
Norfluoxetine	AUC ₀₋₁₂	0.992	(0.965,1.02)
	C _{max} ^{ss}	0.953	(0.918,0.990)

^a The ratio of least-squares means of iloperidone with fluoxetine vs. iloperidone and the 90% confidence interval were obtained from the analysis of logarithmically transformed data.

Conclusions:

Based upon LSMEANS:

1. Iloperidone did not alter the pharmacokinetics and metabolism of fluoxetine and norfluoxetine.

WHAT ARE THE EFFECTS OF DUAL INHIBITION OF PAROXETINE, CYP2D6 INHIBITOR, AND KETOCONAZOLE, CYP3A4 INHIBITOR, ON ILOPERIDONE PLASMA LEVELS

The study was done as a prospective, randomized, open-label, 5-arm study measuring the effect of iloperidone on QTc duration relative to baseline. All patients underwent 5 periods: Screening, Taper, Washout/Baseline, Treatment Period 1 (dose escalation and steady state without metabolic inhibition), and Treatment Period 2 (addition of 1 metabolic inhibitor).

The tablet strength of paroxetine (supplied as Paxil®) used in this study was 20 mg while 200 mg of ketoconazole was used.

Dosing schedule for iloperidone

Dosing schedule:

Period I

Days 1-17- iloperidone 8mg, 12 mg or 24 mg bid

Period II

Days 16-23- iloperidone (8 mg) + paroxetine

Days 18-25 –iloperidone(12 mg and 24 mg) + paroxetine

Period III

Days 24-28- iloperidone (8 mg) + paroxetine+ ketoconazole

Days 26-31 –iloperidone (12 mg and 24 mg) + paroxetine + ketoconazole

Table 26. Average peak concentrations and ratios of average peak concentrations in the presence and in the absence of metabolic inhibitors

Analyte	Average Peak Concentration						Ratio			Ratio		
	Period 1 ^b		Period 2 ^b		Period 3 ^b		(periods 2/1)			(periods 3/1)		
	Mean	CV ^c	Mean	CV	Mean	CV	Mean	N	CV	Mean	N	CV
iloperidone												
ilo 8 mg bid	12.35	57	19.00	53	25.62	42	1.64	25	30	2.34	24	33
ilo 12 mg bid	20.88	43	32.20	44	47.43	55	1.60	31	41	2.29	30	43
ilo 24 mg qd	29.47	39	36.01	56	46.56	41	1.29	29	62	1.54	26	38
P88												
ilo 8 mg bid	18.03	52	28.77	36	44.92	32	1.73	25	35	2.71	24	39
ilo 12 mg bid	24.44	37	36.84	28	54.55	38	1.57	31	25	2.31	30	32
ilo 24 mg qd	33.12	45	39.77	40	60.10	50	1.29	29	37	1.84	27	39
P95												
ilo 8 mg bid	33.39	62	15.15	48	11.01	67	0.50	25	41	0.35	24	62
ilo 12 mg bid	47.22	53	20.83	48	15.89	89	0.52	31	49	0.31	30	50
ilo 24 mg qd	54.59	50	20.43	58	14.44	103	0.43	29	78	0.25	27	78

Note: (a) Average of peak concentrations at steady-state day 1 and day 2. (b) Period 1: no inhibition, Period 2: add one inhibitor, and Period 3: add two inhibitors. (c) CV: coefficient of variation in %.

Plasma samples were collected at the estimated TMAX for iloperidone (parent and primary active metabolite).

Conclusions Period 2 vs Period 1:

1. Compared with peak steady-state concentrations of iloperidone in the absence of inhibition (Period 1), mean peak ratios in the presence of paroxetine (Period 2) increased to 1.60 for the bid regimen.
2. The P88 metabolite ratio increased to 1.57-1.73 from period 1 to period 2.
3. The P95 metabolite decreased to 0.5 from period 1 to period 2.

Conclusions Period 3 vs Period 1:

1. Compared with peak steady-state concentrations of iloperidone in the absence of inhibition (Period 1), mean peak ratios in the presence of paroxetine + ketoconazole (Period 3) increased to 2.3 for the bid regimen.
2. The P88 metabolite ratio increased to 2.31-2.71 from period 1 to period 3.
3. The P95 metabolite decreased to 0.3 from period 1 to period 3.

Conclusions Period 3 vs Period 2:

1 Addition of paroxetine plus ketoconazole resulted in an approximate (1.4-1.5) fold increase in the ratio for bid dosing (i.e., period 2/1 vs period 3/1) for iloperidone and the P88 metabolite

2. There was decrease in the ratio for the P95 metabolite from periods 2/1 to period 3/1 of 1.5 for bid dosing.

HAS THE FINAL MARKETED FORMULATION BEEN SHOWN TO BE BIOEQUIVALENT TO THE CLINICAL STUDY FORMULATION?

The to-be-marketed tablet dosage form was bioequivalent to the clinically studied tablet formulation for iloperidone in a single dose (3x1 mg) crossover fasted BE study.

The to-be-marketed formulation was used in the positive clinical study ILP 3005.

WAS THERE A FOOD EFFECT ?

A 24 subject 3x way crossover study was done to investigate the effect of food and obtain the relative BA of the tablet to an oral solution. Subjects received either 3 x 1 mg iloperidone tablets or a 3 mg oral solution of iloperidone under fasted condition or 3 x 1 mg iloperidone immediately following a high fat meal.

Pharmacokinetic parameters of Iloperidone, P88 and P95 following a single 3 mg dose(3x 1 mg tablets) under fasted and fed conditions are:

Table 27. Results of food effects study

Analyte	Parameter	3 X 1 mg tablets (fasted)	3 x 1 mg tablets (fed)
Iloperidone	AUC ₀₋₂₄ (ng.h/mL)	30.0 ± 17.7	42.4 ± 17.0
	AUC _{0-∞} (ng.h/mL)	44.4 ± 10.7	47.5 ± 10.1
	C _{max} (ng/mL)	3.3 ± 1.5	2.8 ± 0.8
	T _{max} (h)*	2	3
	t _{1/2} (h)	25 ± 10	23.5 ± 5.8
P88	AUC ₀₋₂₄ (ng.h/mL)	64.1 ± 20.7	68.4 ± 17.8
	AUC _{0-∞} (ng.h/mL)	71.8 ± 24.4	74.5 ± 21.2
	C _{max} (ng/mL)	2.9 ± 0.8	2.7 ± 0.5
	T _{max} (h)*	4	6
	t _{1/2} (h)	21.4 ± 8.0	20.7 ± 5.6
P95	AUC ₀₋₂₄ (ng.h/mL)	118.4 ± 47.4	105.3 ± 42.2
	AUC _{0-∞} (ng.h/mL)	130.0 ± 52.1	121.7 ± 48.2
	C _{max} (ng/mL)	3.8 ± 1.8	2.9 ± 1.4
	T _{max} (h)*	6	12
	t _{1/2} (h)	21.4 ± 5.7	22.8 ± 8.2

*= median

Food does not affect the absorption of iloperidone when administered as a 3x 1 mg tablet. There is no effect on either the rate or extent of exposure (C_{max} and AUC_{0-∞}) of iloperidone and its' two metabolites (P88 and P95) when administered in the presence of high fat meal compared to the fasting state. A delay of approximately 1, 2 and 6 h in time to reach maximal concentrations is observed for iloperidone, P88 and P95, respectively.

WHAT IS THE ORAL BIOAVAILABILITY FOR ILOPERIDONE?

A study done in 24 subjects comparing 3x1 mg tablets in the fasted state to a 3 mg oral solution indicated that the tablet is 96% bioavailable.

Analyte	Parameter	3 X 1 mg tablets (fasted)	3 mg solution (fasted)	Tablet/ Solution (%)
Iloperidone	AUC ₀₋₂₄ (ng.h/mL)	30.0 ± 17.7	40.0 ± 17.0	96
	AUC _{0-∞} (ng.h/mL)	44.4 ± 10.7	46.1 ± 20.0	96
	C _{max} (ng/mL)	3.3 ± 1.5	3.8 ± 1.8	87
	t _{max} (h)*	2	1.5	133
	t _{1/2} (h)	25 ± 10	23.4 ± 7.2	107

What is the BCS classification of Iloperidone?

A study done using Caco-2 cells that gave estimates of apparent permeability for apical to basolateral at 120 min of $59.5(\pm 1.8) \times 10^{-5}$ cm/min for iloperidone and for basolateral to apical was at 120 min of $102(\pm 8.4) \times 10^{-5}$ cm/min.

Iloperidone is soluble in organic solvents such as acetonitrile and methanol, moderately soluble in acidic aqueous environments, and sparingly soluble in basic aqueous environments

Since the apparent bioavailability is 96% and the solubility is low, iloperidone should be classified as Class II (Low solubility, High Permeability). However additional validation studies with model compounds would be required to support this classification.

DISSOLUTION

Dissolution Conditions:

Several media were tested including:
USP buffers (pH=3, 4.5 and 6.5) purified water.

The optimal dissolution method conditions and Q proposed by the firm were:
Apparatus 2 (rotating paddle)
500 ml 0.1 N HCl
50 rpm rotation speed.

Q= — in 30 minutes

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The FDA proposed specification for dissolution would be:

Q= ~~—~~ 30 minutes for all strengths of the Tablet

FIRM'S PROPOSED LABEL

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~~X~~ Draft Labeling (b4)

~~X~~ Draft Labeling (b5)

       Deliberative Process (b5)

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SIGNATURES

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