CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-192

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER/ SERIAL NUMBER:	**22-192 / N-0000**
DATE RECEIVED BY CENTER:	9/27/2007
PRODUCT:	Iloperidone
INTENDED CLINICAL POPULATION:	Adults with schizophrenia
SPONSOR:	Vanda Pharmaceuticals
DOCUMENTS REVIEWED:	
REVIEW DIVISION:	**Division of Psychiatry Drug Products (HFD-130)**
PHARM/TOX REVIEWER:	**Sonia Tabacova, Ph.D.**
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Date of review submission to Division File System (DFS): 6/30/2008

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approvable

B. Recommendation for nonclinical studies: Adequate

C. Recommendations on labeling: Changes recommended

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Pharmacology: Iloperidone has high affinity for serotonin 5-HT2A, adrenergic α1, adrenergic α2, D2, D3, and 5-HT1A receptors in humans, and acts as an antagonist at selected dopaminergic, serotonergic, and noradrenergic receptor subtypes. Affinity was highest for 5-HT2 and adrenergic α1 receptors, and lower for dopamine D2, which is a profile of an atypical antipsychotic. Iloperidone metabolites P88 and P89 have a profile similar to that of iloperidone in receptor-binding studies, with potential to exert CNS effects mediated by dopaminergic, serotonergic, and noradrenergic antagonism. P95 exhibits a similar affinity to iloperidone for human 5-HT2A and adrenergic receptor subtypes, while exhibiting a substantially lower affinity for D1, D2, and D3 receptor subtypes compared with iloperidone. P95 is less likely to exert CNS effects since, as shown by whole-body autoradiography, it apparently does not cross the blood-brain barrier. The high affinities of iloperidone and its metabolites for α1- adrenergic receptors in peripheral vascular tissues indicate that iloperidone and its metabolites P88, P89, and P95 are likely to exert cardiovascular effects, such as postural hypotension.

In vitro evaluation of iloperidone effects in isolated dog Purkinje fibers and in mammalian cells expressing the cloned hERG showed that iloperidone has the capacity to prolong action potential duration and to block hERG currents; this indicates that iloperidone has the capacity to prolong QTc interval. Iloperidone metabolite P88, but not P95, also exhibited this potential. In hemodynamic evaluations conducted in rats and dogs, iloperidone was found to dose-dependently decrease blood pressure and to induce transient increases in heart rate; however, cardiac output and ECG parameters were not affected. Neither iloperidone nor its metabolite P95 was associated with any adverse respiratory effects as evaluated in rats.

Pharmacokinetics: Iloperidone was rapidly absorbed in all animal species tested following oral and i.v. administrations, but its bioavailability was very low due to a significant first-pass effect. Oral bioavailability was <1% in rat, 5% in mouse, 19% in both rabbit and dog, and approximately 36% in humans. The absorption profiles of metabolites P88 and P95 were similar to the parent compound; their absorption was rapid after either oral or i.v. administration. At equal oral doses, bioavailability of P95 (18%) was significantly higher than P88 (5%) in mice.

Iloperidone plasma exposure (Cmax and AUC) levels generally increased dose-proportionally in the tested animal species, except for the rat in which exposure increased over-proportionally possibly due to inhibitory activity of iloperidone to CYP enzymes.

Gender differences in exposure were present in the rat, the mean AUC in female rats being significantly greater than that in males.
Distribution of iloperidone and its metabolites after oral administration was rapid; the highest drug concentrations were observed in the liver, kidney, gastrointestinal system, and secretory glandular tissues; placental transfer was limited; and drug concentration in the brain was very low. P95 metabolite did not pass the blood-brain barrier in the rat (whole-body autoradiography). After oral administration to lactating rats, iloperidone was excreted in milk; Cmax was attained 4 hours post dosing when iloperidone concentration was approximately 10 times higher in milk than in plasma.
Iloperidone metabolic profiles show differences across species. The most abundant metabolites in humans (P95 and P88) are found in the species used in toxicology studies. However, in rodents, P95 and P88 are only minor circulating metabolites, in contrast to humans. Plasma exposure to the main active metabolite P88 in rodents and dogs is lower than that of iloperidone, while in humans, P88 exposure is greater than that of the parent compound. For P95, the differences between humans and animals are even greater than for P88. Results of pharmacology and pharmacokinetic studies that have bearing on the potential toxicological characteristics of metabolite P95, include the following:

- While P95 is the predominant circulating metabolite of iloperidone in humans, comprising 25% to 54% of its total metabolism, in rodents it represents only 3.9% to 5.7% of the total measurable exposure to iloperidone and its metabolites.
- Although P95 did not appear to cross the blood-brain barrier as assessed in the whole-body autoradiography study in rats, in general toxicity studies in rodents and dogs with direct oral administration of P95, it induced CNS clinical signs similar to those induced by iloperidone, which suggests that the blood-brain barrier is not impenetrable to P95.
- P95 is rapidly eliminated in rodents; the half-life of P95 is 45 min in mice, 40 min in Sprague-Dawley rats and 100 min in Wistar rats, as compared to a half-life of 23-26 hours for P95 in humans.

In vitro metabolic studies showed that iloperidone has stronger inhibitory activity to CYP2D6 and CYP3A4/3A5 compared with either P88 or P95; neither iloperidone nor its metabolites had potential to induce cytochrome P450 enzymes.
Excretion profiles of iloperidone, P85 and P99 were similar. They are mainly eliminated through the feces, in contrast to humans in which urinary excretion is the major elimination pathway.
Toxicology: Repeat-dose studies of general toxicity and corresponding toxicokinetic parameters were conducted with iloperidone in mice, rats, rabbits, and dogs. Additionally, toxicology studies were performed in rats and mice with the predominant circulating metabolite of iloperidone in humans, P95, to better characterize its safety and toxicity profiles in view of the lower exposure to this metabolite following iloperidone administration in animal species vs. humans.
General toxicology: Among all the repeat-dose general toxicology studies on iloperidone and its P95 metabolite, pivotal studies of the longest duration and therefore most relevant to safety evaluation, are the 6-month rat study and the 12-month dog study conducted with iloperidone, and the 6-month rat study conducted with P95 metabolite. These studies are the subject of the present review.

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