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)

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

Andre Jackson_____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____
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