CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-411

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 2, 2010

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for an approval action for trazodone extended release (ER) tablets for the treatment of major depressive disorder

TO: File NDA 22-411
[Note: This overview should be filed with the 8-10-09 complete response to FDA's 7-17-09 CR letter.]

1.0 BACKGROUND

Trazodone extended release is an extended release tablet formulation of trazodone, a triazolopyridine derivative that is both an SSRI and a 5HT2 antagonist. Trazodone has been marketed worldwide in an immediate release formulation as an antidepressant for almost thirty years. Trazodone ER is available in strengths of 150 and 300 mg (scored tablets), and the sponsor is proposing doses in a range of 150-375 mg/day. This was a 505(b)(2) application that relied on available data from the original application for trazodone IR.

We met with the sponsor for a PreIND meeting on 11-8-06, and held a PreNDA meeting on 2-28-08. We provided comments on the pivotal phase 3 protocol on 8-10-07.

The primary review of the efficacy and safety data was done by Victor Crentsil, M.D., from the clinical group. George Kordzhakhia, Ph.D., from the biometrics group, also reviewed the efficacy data. Kofi Kumi, Ph.D. from OCP reviewed biopharmaceutics data.

The studies supporting this supplement were conducted under IND 76,137, and this supplement was submitted on 9-18-08. We issued a CR action letter on 7-17-09. The major issue holding up approval was a manufacturing site inspection that identified deficiencies needing resolution. We sent draft labeling with the CR letter.

We decided not to take this application to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

All CMC issues for this new formulation have now been resolved.

3.0 PHARMACOLOGY

All pharm/tox issues for this new formulation have been resolved.

4.0 BIOPHARMACEUTICS

Trazodone ER has a very substantial food effect, with an 86% increase in Cmax when taken with food. Thus, labeling will recommend dosing at bedtime, on an empty stomach. The sponsor has agreed to conduct a study to assess any potential for dose-dumping when the drug is taken with ethanol, and this is noted in the AP letter.

5.0 CLINICAL DATA

See my 7-17-09 memo for the CR action for details on the efficacy data submitted for this NDA (results from one additional study), and details of any safety issues that were the subject of our review, since these issues were all resolved in the first review cycle. The sponsor has agreed to both a maintenance study (in adults) and a pediatric depression program in ages 7-17 (both noted in the AP letter). There have been some minor adjustments to labeling since the last review cycle, and we have reached agreement with the sponsor on final labeling.

6.0 CONCLUSIONS AND RECOMMENDATIONS

The final CMC issues have now been resolved, as have all other issues, including agreement on final labeling. Thus, I will issue an approval letter.

cc:
Orig NDA 22-411
HFD-130
HFD-130/TLaughren/MMathis/WBender

DOC: Laughren_NDA22411_TrazodoneER_MDD_AP Memo.doc

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22411	ORIG-1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

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/s/

THOMAS P LAUGHREN
02/02/2010