

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-860

OFFICE DIRECTOR MEMO

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS

DEPUTY DIRECTOR MEMORANDUM

NDA	NDA 21-860
Type of Application	Complete Response to Approvable Action
Applicant	Warner Chilcott, Inc.
Proprietary Drug Name	Sarafem [®]
Established Drug Name	Fluoxetine hydrochloride
Indications	Treatment of premenstrual dysphoric disorder
Route of Administration	Oral
Dosage Form	Tablet
Dosage Strength	Fluoxetine 10, 15, and 20 mg
Dosing Regimen	10, 15, or 20 mg daily in continuous or intermittent luteal phase dosing regimens

Background

Fluoxetine (Prozac[®]) was initially approved for major depressive disorder in 1987, under NDA 18-936, submitted by Eli Lilly. The indication for premenstrual dysphoric disorder (PMDD) was approved in 2000 as a continuous dosing regimen (efficacy supplement No. 058, Sarafem[®]) and as an intermittent dosing regimen in 2002 (efficacy supplement No. 067). The Applicant submitted an NDA for a new tablet formulation of Sarafem[®] and for a new intermediate dose of 15 mg on May 19, 2005. Due to unaddressed labeling issues relating to a change in packaging submitted on the last day of the review cycle, an Approvable Action was taken on March 20, 2006. The Applicant subsequently submitted a Complete Response on March 22, 2006.

Content of Original Application and Findings

The original NDA submission consisted primarily of a single bioequivalence study, other in vitro biopharmaceutical data, chemistry (CMC) data, and labeling.

The single bioequivalence study, Protocol PR 10603.1, was a randomized, single dose, two-period crossover study in which subjects received either a 20 mg tablet (proposed formulation) or 20 mg pulvule (approved formulation) of fluoxetine in Period 1 followed by the other formulation in Period 2. Based on the findings of this study, the Clinical Pharmacology Reviewer (Dr. Apparaju) concluded that the proposed 20 mg tablet formulation had met the criteria for bioequivalence to the approved pulvule.

The Clinical Pharmacology Reviewer also concluded that the Applicant's request for a waiver for demonstrating clinical bioequivalence of the 10 and 15 mg tablets was justified based on:

- demonstration of bioequivalence for the highest dose (20 mg tablet)
- proportionally similar composition of the new 10 and 15 mg tablets in relation to the 20 mg tablet
- comparable dissolution profiles of the lower strength tablets to the 20 mg tablet

Other non-clinical review disciplines (chemistry and toxicology) as well as the primary Medical Reviewer (Dr. Furlong) and the Medical Team Leader (Dr. Soule) also concluded that the Application was approvable subject to acceptable labeling.

Complete Response

On March 22, 2006, the Applicant submitted a Complete Response to the prior Approvable Action that consisted of revised labeling and a safety update. Acceptable labeling was received from the Applicant on May 15, 2006. However, the Division subsequently requested minor editorial revisions to the Package Insert. These revisions were submitted by the Applicant on May 18, 2006 and found to be acceptable.

Regulatory Action

The risk/benefit ratio for the new tablet formulation (and the intermediate dosage strength) is expected to be the same as that for the previously approved pulvule formulation and is therefore acceptable for the indication of PMDD. All reviewers, including both the primary Medical Reviewer (Dr. Furlong) and the Medical Team Leader (Dr. Soule), have recommended approval of NDA 21-860 subject to acceptable product labeling. Acceptable labeling has been submitted by the Applicant.

NDA 21-860 (10, 15, and 20 mg fluoxetine hydrochloride oral tablets) can be approved for the indication of treatment of premenstrual dysphoric disorder.

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Scott Monroe
5/19/2006 03:11:55 PM
MEDICAL OFFICER