

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 18-936/S-054

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

IND/NDA: N18-936 166.1
SPONSOR: Lilly
DRUG: Fluoxetine
DRUG CATEGORY: Selective serotonin reuptake inhibitor **APR 30 1999**
MATERIAL SUBMITTED: Supplement for 40 mg and 60 mg capsules
CORRESPONDENCE DATE: 2/17/99
DATE RECEIVED: 2/18/99

On 12/16/98, this Division issued a Not Approvable (NA) letter for supplement 54, which provided for two new capsule strengths, 40 mg and 60 mg. In the NA letter, the sponsor was asked to conduct an in vivo bioequivalence study using the 60 mg strength; with this, a waiver would be possible for an in vivo study of the 40 mg strength. A meeting with representatives of Lilly was held on 2/5/99 regarding the NA letter. At that time the sponsor indicated that they did, in fact, have some in vivo pharmacokinetic data for the 60 mg capsule, from a study designated Protocol 38, and they were encouraged to submit these data. This submission is in response.

Please refer to the Biopharmaceutics review dated 4/21/99 by Dr. Yuan. As part of study 38, conducted some years ago, four subjects received the to be marketed 60 mg capsule simultaneously with 30 mg of deuterium labeled fluoxetine solution, and 4 subjects received a fluoxetine 20 mg capsule simultaneously with 20 mg of deuterium labeled fluoxetine solution. This technique permits simultaneous comparison of pharmacokinetic parameters for labeled and unlabeled drug. With this, the 60 mg capsule meets criteria for bioequivalence for parent drug, but not for norfluoxetine.

Conclusions and recommendations: Although the sample size is very small; i.e., only four subjects received the to-be-marketed 60 mg capsule, the data from Protocol 38 meet the statistical requirements for bioequivalence, for the parent drug. There are other considerations that one may consider as mitigating the limited in vivo data for this new capsule strength; namely, the fact that fluoxetine is regarded as highly permeable and highly soluble, and the wide therapeutic index for fluoxetine. From a clinical standpoint this supplement is approvable.

ISI

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NDA 18-936
Div file
HFD 120/TLaughren/AMosholder/PDavid/RYuan

4-30-99
This supplement
can now be
approved.
ISI
TL, PDP

REVIEW AND EVALUATION OF CLINICAL DATA

IND/NDA: N18-936
SPONSOR: Lilly
DRUG: Fluoxetine OCT 16 1998
DRUG CATEGORY: Selective serotonin reuptake inhibitor
MATERIAL SUBMITTED: Supplement for 40 mg and 60 mg capsules
CORRESPONDENCE DATE: 6/17/98
DATE RECEIVED: 6/18/98

This supplement is an application to market 40 and 60 mg capsules of fluoxetine (Prozac), which is currently available in 10 mg and 20 mg capsules. The proposed labeling for these new dose strengths involves changes to the Description and How Supplied labeling sections. No changes are proposed for the Dosage and Administration section of labeling, and a dosage of 40 or 60 mg is within the recommended range (that is, up to 80 mg as a single daily dose). The submission consists of chemistry, manufacturing and controls information, and in vitro dissolution data. No in vivo pharmacokinetic bioequivalence study was conducted.

Conclusions and recommendations: There are no clinical data or labeling changes involved, so from a clinical standpoint, the supplement may be approved (assuming that it is acceptable to the Biopharmaceutics and Chemistry review teams, of course).

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NDA 18-936
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10-16-98
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