CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-520

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 21-520 Symbyax™ (Olanzapine and Fluoxetine Combination)
Review number: 2
Sequence number/date/type of submission:
June 24, 2003 / SSN

Information to sponsor: Yes
Sponsor and/or agent: Eli Lilly and Company
Manufacturer for drug substance:
Lilly del Caribe, Inc.
Puerto Rico Industrial Park
Carolina, Puerto Rico 00985

Reviewer name: Sonia Tabacova, Ph.D.
Division name: DNDP
HFD #: 120
Review completion date: December 18, 2003

Drug:

Trade name: SYMBYAX™
Generic name: Olanzapine and Fluoxetine hydrochloride combination
Chemical name:
Olanzapine: *2- methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b] [1,5]benzodiazepine*
Fluoxetine : *(±)-N-methyl-3-phenyl-3-[(α,α,α -trifluoro-p- tolyl)oxy]propylamine hydrochloride*

Relevant INDs/NDAs/DMFs: NDA 21-520 Symbyax™ (Olanzapine and Fluoxetine Combination)

Background: The present resubmission contains the sponsor's complete response to FDA approvable letter for NDA 21-520, including response to comments and requests in the approvable letter and responses to comments from the annotated FDA proposed package insert. This review covers non-clinical pharmacology and toxicology issues of sponsor's responses.

I. Review of sponsor's response to non-clinical pharmacology and toxicology comments and requests in the approvable letter

I.1. Re Lilly response to FDA proposal for prenatal and postnatal development study in rats as a Phase 4 commitment

The sponsor states that the basis for the FDA request to conduct a repeat of the prenatal/postnatal development study in rats as a Phase 4 commitment "appears to stem from a difference in interpretation of the testicular effects observed in F1 male rats whose mothers received the low-dose combination...versus the vehicle control group". The sponsor states that "there is no evidence of a treatment-related testicular degeneration and/or atrophy in F1 rats in the low-dose combination group" and that "the few individual cases of testicular degeneration present in this group were not different from those occasionally seen in control rats of this strain and age", and provides a table showing the similarity with the background incidence rate of testicular degeneration in in-house fertility studies using the CD rat.

However, there are clear changes in the F1 male reproductive system at the low-dose combination (high-dose combination not tested for these endpoints) in comparison to the control group in the same study, as well as to the groups treated with equivalent doses of fluoxetine or olanzapine alone. As indicated in our original review of NDA 21-520, p. 61-64, "mean epidydimal and seminal vesicles weights in the low-dose combination group were significantly lower in comparison to control, while no

significant differences were seen in fluoxetine- or olanzapine-alone groups; mean testicular weight relative to body weight was also lower in the low-dose combination group in comparison to all other groups". "Histopathologically, testicular tubular degeneration or atrophy was found in 4 males, and severe depletion of epidydimal sperm or aspermia, in 2 males of the low-dose combination group; no such findings were seen in the other groups except for one case of slight multifocal testicular tubular degeneration in fluoxetine group". In addition, "the males in the low-dose combination group had cauda epididymal sperm concentration lower (although not significantly so) in comparison to control values" and although no significant differences were found in sperm motion parameters between the control group and the low-dose olanzapine-fluoxetine combination groups, "two rats, 4052M1 and 4054M1, in the low-dose combination group were excluded from sperm motion and concentration analysis. These rats exhibited small testes and epididymides and the sponsor considered them not representative of the group. No justification was provided for this conclusion".

The FDA recommendation for a repeat of the prenatal/postnatal development study in rats as a Phase 4 commitment is based on these findings as well as on the fact that no meaningful toxicological conclusions about these (and other) developmental endpoints in F1 generation can be made on the basis of the submitted postnatal developmental study. This study employed only two olanzapine/fluoxetine combination (OFC) dose levels: high and low. The high dose combination induced excessive mortality in the progeny early in life that did not allow assessment of postnatal developmental endpoints other than survival and body weight. For this reason, the sponsor did not provide data on developmental endpoints in the progeny (including those of the reproductive system) at the HD combination. No proper toxicological assessment or meaningful conclusion about OFC postnatal developmental toxicity can be made based on the available results at only one (LD) dose level. In conclusion, there is obviously a need for a repeated pre/postnatal study (as a phase 4 commitment) with a more appropriate dose selection that would allow a reliable assessment of postnatal developmental toxicity parameters and their dose-effect relationships and NOAEL.

II. FDA responses to the labeling changes from Lilly Proposal in June 24 Complete Response

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FDA Comment: *Accepted with corrections (correction included in the corresponding paragraph in December 11, 2003 PI as reproduced below):*
In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high-dose combination of olanzapine and fluoxetine [5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/m2 basis), respectively] and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m^2 basis).

5.
Pregnancy –Pregnancy Category C

SYMBYAX

FDA Comment: *Accepted with corrections (correction included in the corresponding paragraph in December 11, 2003 PI as reproduced below):*
SYMBYAX Embryofetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4

mg/kg/day (low dose) (1 and 0.5 times the MRHD on a mg/m^2 basis, respectively) and 4 and 8 mg/kg/day (high dose) (2 and 1 times the MRHD on a mg/m^2 basis, respectively). In rabbits, the doses were: 4 and 4 mg/kg/day (low dose) (4 and 1 times the MRHD on a mg/m^2 basis, respectively) and 8 and 8 mg/kg/day (high dose) (9 and 2 times the MRHD on a mg/m^2 basis, respectively).

6.
In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity.

7.
In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination [low-dose: 2 and 4 mg/kg (1 and 0.5 times the MRHD on a mg/m^2 basis), respectively, high-dose: 4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m^2 basis) respectively] and alone [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m^2 basis), respectively]. Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone.

FDA Comment: *Accepted*

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10.

Our proposed labeling changes in section "Drug abuse and dependence" (see below) were not included in the labeling sent to sponsor on December 11/ 03.

DRUG ABUSE AND DEPENDENCE

Controlled substance class — SYMBYAX is not a controlled substance.

Physical and psychological dependence — SYMBYAX, as with fluoxetine and olanzapine, has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical studies did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SYMBYAX (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Recommendations

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3. Recommended labeling:

The pharm/tox labeling corrections pertain to the following sections: Impairment of Fertility; Pregnancy - pregnancy category C; and Drug abuse and dependence.

Impairment of Fertility

SYMBYAX – Fertility studies were not conducted with SYMBYAX. However, in a repeat-dose rat toxicology study of three months duration, ovary weight was decreased in females treated with the low-dose (2 and 4 mg/kg/day [1 and 0.5 times the MRHD on a mg/m^2 basis], respectively) and high-dose (4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively) combinations of olanzapine and fluoxetine. Decreased ovary weight, and corpora luteal depletion and uterine atrophy were observed to a greater extent in the females receiving the high-dose combination than in females receiving either olanzapine or fluoxetine alone. In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high-dose combination of olanzapine and fluoxetine [5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/m2 basis), respectively] and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m^2 basis).

Olanzapine — In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male-mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m^2 basis). Diestrous

was prolonged and estrous was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis); therefore, olanzapine may produce a delay in ovulation.
Fluoxetine — Two fertility studies conducted in rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility.

Pregnancy—Pregnancy Category C

Olanzapine

In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m^2 basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m^2 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including two resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, three therapeutic abortions, and one spontaneous abortion.

Fluoxetine

In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m^2 basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis). Labor and Delivery

SYMBYAX

The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was not affected by SYMBYAX. SYMBYAX should be used during labor and delivery only if the potential benefit justifies the potential risk.

Olanzapine

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

Fluoxetine

The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placenta; therefore, there is a possibility that fluoxetine may have adverse effects on the newborn.

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DRUG ABUSE AND DEPENDENCE

Controlled substance class — SYMBYAX is not a controlled substance.

Physical and psychological dependence — SYMBYAX, as with fluoxetine and olanzapine, has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical studies did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SYMBYAX (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

In studies in rats and rhesus monkeys designed to assess abuse and dependence potential, olanzapine alone was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence at oral doses up to 15 (rat) and 8 (monkey) times the MRHD (20 mg) on a mg/m^2 basis.