

MAR 23 1985

SAFETY REVIEW OF NDA 18-936

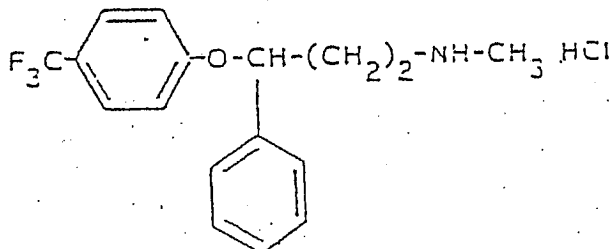
Sponsor: Eli Lilly and Company
307 East McCarty Street
Indianapolis, IN 46285

Drug: fluoxetine HCl

Category: antidepressant, a non-tricyclic phenylpropylamine

1.0. Introductory Overview

1.01 Description of the Compound

Chemical StructureChemical Names (USAN):

- (1) Esazenepropranamine, N-methyl-γ-
[4-(trifluoromethyl) phenoxy]-,
(±)hydrochloride.
- (2) (±)-N-Methyl-3-phenyl-3-[(α,α,α-trifluoro-p-
tolyl)oxy]propylamine hydrochloride

Molecular Formula: $\text{C}_{17}\text{H}_{18}\text{F}_3\text{NO} \cdot \text{HCl}$

Molecular Weight: 345.79

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1.02 Resume

Fluoxetine is a straight-chain phenyl propylamine which inhibits uptake of serotonin into neurons. It does not affect noradrenergic or dopaminergic neurons.

Fluoxetine appears to be a relatively safe drug. Of 76 significant adverse clinical events occurring among patients exposed to fluoxetine, as reported in this NDA, only 6 cases of allergic-type skin reactions were probably attributable to the effect of this new drug. Other than these hypersensitivity reactions, 2 cases of seizures, 4 cases of movement disorders, 10 cases of psychotic episodes, and 13 cases of abnormal laboratory parameters may perhaps have been caused by fluoxetine. In none of these cases, however, was the frequency of adverse event or the circumstances of the patient such that the adverse effect would clearly be attributed to the drug.

Nevertheless, fluoxetine did effect two physiologic parameters: hemoglobin and LDH. Among 8% of patients exposed to fluoxetine, it appeared to induce a mild to moderate decrease in hemoglobin level and to cause elevations of LDH at about the same rate. In the former case, fluoxetine reduced hemoglobin more frequently than did imipramine or placebo, while in the case of LDH, it caused elevations at a rate higher than placebo but equal to imipramine.

Fluoxetine tends to induce a group of side effects significantly different from standard tricyclic antidepressants. Rather than producing anticholinergic effects and sedation, most frequently this new drug caused nausea, insomnia, and nervousness, which resembles the profile of a stimulant rather than a sedative drug. Indeed it produced more diarrhea than constipation, and in one controlled study demonstrated potency as an appetite suppressant. It is fluoxetine's particular profile of side effects which may perhaps, in the future, give rise to the greatest clinical liabilities in the use of this medication to treat depression. Depressed patients often suffer from insomnia, nervousness, anorexia, and weight loss as a result of their primary illness. Fluoxetine may possibly exacerbate these vegetative signs. Among elderly, cachectic, anorexic, or physically ill patients, fluoxetine's tendency to cause loss of appetite, perhaps leading to a reduction of dietary intake, may produce serious consequences.

In general, however, fluoxetine does not appear to cause serious toxicity at the dosage level employed in this NDA, up to 80 mg/day. It showed little adverse effect on cardiovascular function, liver function, and most other laboratory parameters. If significant amelioration of depression is a demonstrable effect of this drug, this benefit would appear to outweigh any potential risks associated with its clinical use which became evident among patients exposed to fluoxetine reported in this NDA.

1.17 Duration on Fluoxetine

The Company provided the following breakdown of its total fluoxetine cohort by length of exposure as follows (Vol. 1.76, p. 025):

Table 2

<u>No. of Days</u>	<u>No. of Patients</u>
<14	1173
14-30	1009
31-90	774
91-182	393
183-365	218
>365	74*

*Three dystonia musculorum deformans patients have been on fluoxetine for more than two years, one of them for more than four years.

1.2 Non-Domestic Marketing Experience

Fluoxetine has not been marketed outside the U.S.A. However, the company is presently engaged in studies overseas with the motive of eventual marketing. To date all adverse events occurring overseas have been submitted to IND.

1.3 Catastrophic and Serious Events and Seriously Abnormal Laboratory Findings

In general these adverse events were reported by the Company in the individual safety summaries or in a special section of events "requiring further comment."

In addition, such reactions were discovered by reviewing all the laboratory data and all the early termination summaries of patients participating in late Phase II and Phase II $\frac{1}{2}$ clinical trials. 52 cases were selected where laboratory values were egregiously abnormal or reasons for early termination caused concern. These 52 cases were then subjected to review of case reports on microfiche. Certain additional adverse events, not reported by the Company, which were revealed on microfiche, are also included in this tabulation. In most cases, these adverse events involved the onset of an unreported psychotic episode.

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1.31 Phase I Events

Only one possibly serious adverse event occurred among the 116 normal subjects in Phase I trials. One patient was reported to have had a "mild seizure" on day 12 of fluoxetine therapy, while participating in the 30 day multiple dose Study #4. The seizure and the patient were not further characterized.

1.32 Early Phase II Events

Among 77 patients with major depression exposed to fluoxetine in early open label studies, there were five serious clinical events. One patient had a severe dystonic reaction and a second developed a palpable thyroid gland and liver, with a scaly rash on his legs. A third patient developed squamous cell carcinoma of the lung while in the study. Lastly, two patients had psychotic episodes; one was described as paranoid, the other as a case of mania.

1.33 Late Phase II and Phase III Events

Among 688 patients exposed to fluoxetine in late Phase II/Phase III clinical trials, serious adverse events occurred in 33 patients.

The onset of a psychotic episode occurred in 4 patients.

Two patients committed suicide, both males, aged 30 and 45 years, one by overdose of phenelzine, and the other by hanging. Four other patients attempted suicide and recovered. In 2 of these non-fatal cases fluoxetine was among the drugs taken in overdose, and the highest known fluoxetine overdosage among these 2 cases was 80 mg.

Two patients had seizures. In one case, the seizure followed an overdose of Darvocet. In a second case, the patient reported the seizure to the investigator who believed it was "psychogenic".

Four patients developed movement disorders of various kinds: One had dyskinesic jaw movements; one had involuntary movements of the face and arms; one had sleep myoclonus; one had a "thick and quivering" tongue.

Two patients had allergic skin reactions requiring hospitalization. One elderly woman, who was also taking chloral hydrate and other medicines developed a widespread pruritic maculopapular rash, with a white count of 19,700 with 15% eosinophils. She was diagnosed as having a hypersensitivity reaction to fluoxetine. A second woman, 26 years old, had a sudden onset of rash accompanied by fever, arthralgia and nausea. The rash was "typical of erythema multiforme." Both women recovered following discontinuation of fluoxetine.

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Movement Disorders - Four patients developed movement disorders. In one of these cases, fluoxetine seemed to aggravate a pre-existing condition, Dystonia Musculorum Deformans.

Neoplasms - There was one case of squamous cell carcinoma of the lung, one case of colon carcinoma, and one case of chronic lymphocytic leukemia, among patients exposed to fluoxetine.

GYN - Two patients had episodes of vaginal bleeding and one patient developed amenorrhea and galactorrhea.

Hypersensitivity - There were twelve cases of allergic type skin reactions. Two of these required hospitalization. Six cases may have been related to concomittant drugs or other factors besides fluoxetine.

Clinical Laboratory - There were 2 cases of elevated SGOT and 3 cases of elevated alkaline phosphalase.

There were 17 cases of low white count. Nine of these cases may have been the result of lab error as they all occurred in a numerical sequence in one study. Of the remaining 8 cases, only 3 patients had white counts below 3000, while five were between 3500 and 3000.

There were four other miscellaneous abnormalities among fluoxetine patients.

2.0 Summary of the Major Drug Associated Risks

There appears to exist no convincing evidence for any major risk associated with the use of fluoxetine. Nevertheless, it is true that two laboratory parameters may possibly have been affected by the drug: hemoglobin and LDH. The clinical significance of these effects is not clear at the present time. In addition, fluoxetine has been shown frequently to produce negative effects including nausea, insomnia, nervousness, anorexia, and weight loss. These signs and symptoms are often concomittants of severely depressed mood. It is possible that administration of this drug might exacerbate one or more of these vegetative phenomena. The significance and details of these potential adverse effects are discussed below, following the section on methodology.

2.1 Methods of Assessment

In order to carry out a thorough inspection of this NDA submission and to review the data for evidence of major drug associated risks, the following procedures were used:

Each individual safety summary for each separate study was reviewed and noted.

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2.24 Insomnia, nervousness, anorexia, and weight loss.

Unlike standard tricyclic antidepressants, fluoxetine's profile of adverse effects more closely resembles that of a stimulant drug than one that causes sedation and gain of weight. Among treatment emergent signs and symptoms, the most common effects produced by fluoxetine included nausea, insomnia, and nervousness. Indeed nervousness was the most common adverse symptom cited by long-term fluoxetine patients who eventually discontinued therapy due to an adverse reaction. (See Section 3.1 of this review, and Appendix Tables XIV through XIX.) In addition, fluoxetine is known to suppress appetite and produce loss of weight as demonstrated in one double-blind study of obese patients. (See Section 3.23 of this review.)

It is possible that these adverse effects of fluoxetine treatment may negatively affect patients with depression. Since depressed patients frequently suffer from insomnia, nervousness, anorexia, and weight loss, it is possible that fluoxetine treatment might, at least temporarily, make their illness worse. Among elderly, cachectic, anorexic, or physically ill patients, reduction of nutritional intake may have serious consequences; and perhaps such an effect is related to the decrements of hemoglobin discussed above.

Nevertheless the severity of the risk posed by these effects does not appear great. Among patients who terminated fluoxetine studies prematurely (presumably the ones who had the most severe negative reactions) no patient was reported to have suffered loss of weight. Moreover no patients in the study of geriatric patients suffered weight loss. However, 25% of fluoxetine patients who terminated prematurely did report nervousness, while 20% reported insomnia, and 5% complained of poor appetite (see Appendix Table II). At the present time, it does not appear that any serious risk results from these adverse effects, and such risk as does occur may be easily managed by discontinuing or changing the treatment.

From a regulatory point of view, it would appear that no stringent action is required to deal with this problem. However it may be appropriate to develop advisory labelling warning the physician that certain signs and symptoms of depression may be exacerbated by this drug. If the drug is marketed, post-marketing studies should be required to determine the frequency with which fluoxetine may cause intensification of these specific signs and symptoms of depressive illness.

2.25 Summary of Section 2.2

In conclusion, it appears that there may be three possible safety risks and one possible benefit associated with fluoxetine. Patients exposed to this drug show higher rates of reduced hemoglobin than do patients on placebo or imipramine, and there may also be a fluoxetine-induced elevation of LDH. It is not clear whether any of these alterations reflect clinically significant changes. It is possible that adverse effects

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3.6 Summary of Section 3

Fluoxetine differs significantly from standard tricyclic antidepressants in its profile of adverse effects and in altering certain physiologic parameters. The most striking adverse effects, and the ones most likely to affect future patients who may be treated with fluoxetine for depression, are nausea, insomnia, anxiety, nervousness, anorexia, and weight loss. Depressed patients are often nervous, anxious, and sleepless, and they have often experience loss of appetite and weight. It be possible, therefore, that fluoxetine may exacerbate certain depressive symptoms and signs. Potentially, the most debilitating of these effects may involve weight loss. Among elderly, cachectic, anorexic, or physically ill patients, reduction of dietary intake might have serious consequences. These problems should be examined in future studies of fluoxetine.

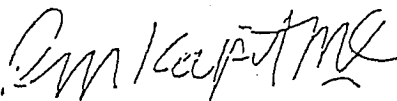
In addition, it is important to note that the verdict is not in on the ophthalmologic safety of this drug. The Company described only 3 of 30 abnormal eye findings among patients exposed to fluoxetine, asserting that all the other abnormalities were not drug-related.

4.0 Overall Conclusion and Recommendations

Fluoxetine appears to be a relatively safe drug. If it can be demonstrated that treatment with fluoxetine significantly benefits patients with depression, it would appear that the benefits of fluoxetine treatment would substantially outweigh the risks associated with taking this drug.

Certain clinical risks of mild to moderate severity did appear to be associated with the use of fluoxetine, as determined by a review of the safety data in this NDA submission. These potential risks include intensification of the vegetative signs and symptoms of depression, reduction of hemoglobin level, and elevation of serum LDH.

It is suggested that labelling be developed which advises physicians about possible exacerbation of the vegetative manifestations of depressive illness and about the possibility of decreases in hemoglobin. The occurrence of LDH elevations should be mentioned. If the drug is marketed, post-marketing studies should be required to assess more precisely the severity of these potential risks.



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