To Laughren
as Cal rpt
on 9/12/20

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: SEP 11 1990

FROM: Chief, Epidemiology Branch, HFD-733

SUBJECT: Meetings on experience from fluoxetine surveillance: September 18 (in-house) and September 25 (with firm)

THROUGH: Acting Director, CR 9/11/90
Office of Epidemiology and Biostatistics, HFD-701

TO: Director,
Division of Neuropharmacologic Drug Products, HFD-120

Attached are three documents which have been prepared by Epidemiology Branch staff as background for the subject meetings:

1. A memorandum to you from Dr. David Graham, which reviews the sponsor's July 17, 1990 submission entitled "Summary of Post Marketing Safety Experience."

2. A report by Drs. Franz Rosa and Carlene Baum of findings from in-house analysis of Ohio Medicaid data, entitled "Medicaid Diagnoses Before and After Starting Fluoxetine."

3. An update by Dr. Robert Wise on "Fluoxetine Increased Frequency Report Submissions."

I wish to expand here on the last paragraph of page four of Dr. Graham's memorandum, which refers to the sponsor's exclusion of 76 cases from the suicidality analyses presented in the July 17, 1990 submission in Table VIII.2. (page 42276) and Table VIII.4. (page 42278):

> In the analyses of suicidality, 76 of the total of 97 cases were excluded because they occurred in compassionate use studies or other studies which did not have controls. It is inappropriate in a safety analysis to exclude such a large proportion of cases. A fluoxetine suicidality rate should be computed for the uncontrolled studies and compared to the rate for the controlled studies, which is 21 cases/3333 users, or about 0.6 percent (representing 9 cases/1741 users in the depression studies and 12 cases/1592 users in the non-depression studies, p= 0.39, two-sided test for equality of rates). If the

suicidality rates do not differ significantly between the uncontrolled studies and the controlled studies, an overall rate should be used in the comparisons with other drugs (and in the estimation of sample size requirements for future research.) If the rates do differ significantly, the groups of fluoxetine users upon which they are based should be studied further in a effort to identify pre-treatment risk factors for the emergence of suicidality during fluoxetine use. Finally, I recommend that suicidality case-control analyses nested in these and other cohorts of fluoxetine users be performed for investigation of pre-treatment risk factors.

Bruce V Stadel

Bruce V. Stadel, MD, MPH

cc:

HFD-120/Laughren/Brecher
HFD-700/Anello
HFD-733/Stadel/Graham/Rosa/Baum/Wise
HFD-735/Barash
NDA # 18,936
DRU 1.7 fluoxetine
Chron

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: OCT 11 1990

TO: Director, Division of Neuropharmacologic Drug Products (HFD-120)

THROUGH: Acting Director, Office of Epidemiology and Biostatistics (HFD-700) ca 9/11/9

SUBJECT: Sponsor's ADR submission on fluoxetine dated July 17, 1990

FROM: Section Chief, Epidemiology Branch (HFD-733)

The sponsor was asked by the reviewing division to analyze and discuss postmarketing data on fluoxetine for its first two years of marketing relating to several different potential reactions. The report submitted by the firm addressed eight reaction entities and included a review of both IND clinical trial experience and domestic spontaneous adverse reaction reporting.

Eosinophilia. Eosinophilia was noted in 19 fluoxetine and 14 placebo patients during IND studies. Two fluoxetine and one placebo patient developed rash in association with eosinophilia, and one other fluoxetine patient developed associated fever. The study group sizes were 2044 fluoxetine and 1397 placebo patients.

From postmarketing data, there were 17 reports of eosinophilia. Eight had eosinophilia-myalgia syndrome or someching resembling it. Three of these eight had concomitant L-tryptophan and the remaining five did not. The firm concluded that there was no pattern suggestive of eosinophilia-myalgia syndrome in this data. While it is true that CDC has epidemiologically linked eosinophilia-myalgia syndrome to a single Japanese manufacturer of L-tryptophan and has postulated that the syndrome may be due to a contaminant, this does not explain the five cases reported with eosinophilia and arthralgia or myalgia, with or without fever occurring in the absence of L-tryptophan.

Guillain Barre Syndrome (GBS). In its introduction to this section, the sponsor noted that zimelidine, a serotonin uptake inhibitor, was associated with GBS and this led to its withdrawal. Because fluoxetine is also a serotonin uptake inhibitor, the firm was interested in pursuing this. The firm reported seven cases, of which they consider three to be probable or definite, two unlikely and two uncertain because of incomplete follow-up or data. In reviewing the material submitted, one of the cases labeled unlikely by the sponsor may be a true case. Case 6 is compatible with the diagnosis of GBS in that rapidly progressive extemity weakness was associated with a demyelinative EMG/NCV.

The firm cited background rates for GBS of 0.6 to 1.9 per 100,000 per year and with an estimated 2.1 million fluoxetine exposed patients (method of this estimation not described), concluded that there was no trend in the data to suggest an association.

Several issues are important to consider because they may necessitate a change in this conclusion. First, underreporting of adverse reactions is not addressed by the firm and may have substantial effect here. Second, the incidence rates cited by the sponsor are based on 100,000 person-years of observation. In its analysis, the firm has implicitly assumed that the estimated 2.1 million patients treated with fluoxetine all received it for one year. From other work we have done with antidepressants in the past, this is probably not a valid assumption. Finally, in reviewing the case material provided, duration of therapy for most was about two months or less. The risk of drug-induced GBS is usually confined to some initial period of exposure, after which it falls to background levels. This is consistent with what is believed to be the underlying immunologic basis for the reaction.

Average Duration Therapy	Person-Years Accrued	Expected Cases Background Rates 0.6	1.9
1 month	180,000	1.1	3.4
3 months	500,000	3.0	9.5
6 months	1,000,000	6.0	19.0
12 months	2,100,000	12.0	38.0

This table shows the "expected" number of GBS cases in a population of 2.1 million people followed for varying durations of time up to one year if the background rate for disease is 0.6 or 1.9 per 100,000 per year. From spontaneous reports we have 3-5 cases by the firm's estimate and 4-6 by our estimate. Given that underreporting may be substantial, that most cases had GBS onset by two months of therapy, and that only some initial period of time on drug is important to reaction onset, it seems possible that fluoxetine use might be associated with GBS occurrence.

Hyponatremia. The firm stated that one case of hyponatremia had been reported as an ADR during IND studies in 6630 patients, but that serum sodium was not routinely checked so that effects of drug on serum sodium could not be evaluated from these patients. From spontaneous sources, 20 cases were reported through September 1988 (covering 8 months of marketing). The firm also presented reports from the scientific literature showing that both serotonin and fluoxetine increase ADH levels in experimental animals. The firm mentioned that possible SIADH is in the product label.

Monoamine oxidase inhibitor (MAOI) interactions. IND studies were reviewed for patients who took fluoxetine and MAOI's in close temporal proximity or concurrently. This included 16 patients on phenylzine, 24 on tranylcypromine and 17 on isocarboxacid. Among these, there were two patients with myoclonus, two with somnolence, one with syncope and one with orthostatic hypotension. Spontaneous reports through November 1989 included 5 fatal and 1 non-fatal case of fluoxetine/MAOI interaction. Studies in rats have also shown that

hyperpyrexia can result from this interaction. The firm states this interaction is described in product labeling and that because of the long half-life of metabolites, that MAOI's should not be used in patients until after they have been off fluoxetine for at least five weeks.

Pulmonary events. The firm reviewed its IND and postmarketing experience through mid-June 1989, for the reporting of a variety of pulmonary reaction terms and noted that a number of cases suggestive of an "inflammatory" or "allergic" mechanism had been reported. It commented that many of these cases were complex but some had occurred in otherwise healthy people. For the majority, the only presenting symptom was dyspnea. "Many" had symptom resolution with discontinuation of fluoxetine and the addition of steroids in some. No discussion was directed at those who did not have resolution of symptoms. The firm also noted that the estimated reporting rate for pulmonary events had declined over time. It concluded by drawing a connection between immune-mediated or vasculitic rash reactions and pulmonary events, suggesting a spectrum of hypersensitivity responses to the drug.

Reporting rates do not translate into incidence rates because there is probably substantial underreporting of events. The three-fold decline in reporting rates by quarter of marketing seen in two years provides evidence of this. The firm's analysis does not separate serious from non-serious pulmonary events and does not discuss the presence or absence of fatal cases. The firm stated it has modified the product label to include some reference to "other allergic events." Dyspnea is generally the only symptom present in patients taking fluoxetine who develop drug-induced pulmonary disease. We believe dyspnea is at least as important as rash as an indication of an immune/hypersensitivity reaction. The firm has included in product labeling the recommendation to discontinue fluoxetine upon the appearence of rash. Dyspnea, as the most important, and usually only symptom of allergic pulmonary disease is not specifically mentioned as an indication for discontinuation.

Selected hematologic events. The firm received 506 spontaneous reports of hematolgic events possibly related to increased bleeding (4% of all reports), of which 130 (26%) were serious. Concomitant drugs capable of potentially affecting bleeding were present in 11%. Dose did not appear to be a factor, and reports seemed less likely within the first 2 weeks and more common after 8 weeks of therapy. Platelet studies were done in 7 patients. The results shown in table 3 under the column labeled "Epi 2" suggest to this reviewer that both aspirin and fluoxetine have platelet inhibiting properties. The sponsor has reached the opposite conclusion that fluoxetine does not inhibit platelet function. As in other sections of the firm's submission, fatal events were not separately evaluated or commented upon.

Suicidality. The firm reviewed data from IND studies, prefacing it with the acknowledgement that these trials were not designed for the prospective evaluation of suicidality. In these trials, patients with current suicidal ideation were excluded. Suicidal ideation was studied in two ways. The first involved analysis of clinical comments ascertained through non-probing, open-ended questions during the trial. Also, at the beginning and end of the study, patients completed a self-administered questionnaire, the Hamilton Rating Scale for Depression, which included one question on suicide. This question, referred

to as HAMD-3, rated suicidal ideation on an ordinal scale from 0 (absent) to 4 (severe ideation, usually with an attempt). The capacity of these trials to identify and describe the quality and intensity of suicidality was low.

The firm's review covered IND studies through late December 1989. There were 97 reports of suicidality with fluoxetine (21 while in IND trials and 76 during compassionate or open-label use), 9 with placebo and 2 with tricyclic controls. The 76 fluoxetine cases from studies other than double-blind and controlled were excluded from the firm's meta-analysis. Combining all studies (table 8.2), the suicidality rate was 0.517% with fluoxetine, 0.178% with placebo and 0.273% with tricyclic controls. The firm reported these differences were not statistically significant.

In its introductory discussion, the firm called attention to an abstract by Fava and Rosenbaum which "concluded that there were no statistically significant differences among rates of treatment-emergent suicidal ideation associated with five classes of antidepressant therapy." While this is technically correct, the actual data from this retrospective chart-review study do raise some potential questions. The data are shown in the table below.

	Fluox	Fluox + TCA	TCA+/-Li	MAOI or Other
Total treated	294	73	458	192
Pre-existing suicidality	65	13	75	?
Treatment-emergent suicidality	6 (2.9%)	2 (3.3%)	3 (0.8%)	1 (0. %)

Treatment-emergent suicidality was more frequent among "fluoxetine alone" than "tricyclics with or without lithium" patients. The relative risk of suicidality was 3.3 (95% CL 0.9, 12.2), p = 0.07.

There are many problems with this study that cannot be assessed. The distribution of pre-existing suicidality between the fluoxetine and tricyclic groups was different (p = 0.05). This raises the question that the remaining patients not suicidal at baseline in the fluoxetine group may have been more severely depressed than those in the tricyclic group, but this is purely speculative. We also don't know if patient groups were similar or dissimilar with respect to other factors important to suicidal ideation.

Overall, the analysis presented by the firm had several shortcomings which should be noted. In the meta-analysis of suicidality from IND trials, 76 fluoxetine cases were excluded from analysis because the patients were in studies or other trials lacking comparative controls. It can be argued that these exclusions are not justified or appropriate in a meta-analysis where data contributing to both the numerator and denominator of fluoxetine were collected and are analyzable. Were these cases included, substantial differences in suicidality between drugs could have been observed. A related problem is that suicidal ideation was probably viewed as a component of the underlying

depressive disorder and hence frequently not commented upon or noted by research physicians and nurse monitors in the IND studies. This possibility is mentioned by the firm.

Other problems relate to the analysis of HAMD-3 scores. The analyses compared only the start and finish scores, ignoring the possibility of intercurrent suicidality which resolved by the completion of the study. Also, to be counted as a case of suicidality, the patient had to have a HAMD-3 score of 3 or 4, requiring "suggestive behavior" indicative of suicidality or a serious attempt. This may be too stringent a requirement, especially if the goal is to detect increases in or characterize the nature of suicidal ideation.

Violent behavior. The firm began this section with an overview of the prevalence of violent behavior in the United States and juxtaposed this with mention of "fewer than 10" spontaneous reports of violence among fluoxetine users. This cannot be interpreted to mean that fluoxetine reduces the occurrence of this behavior as implied by the firm. Rather, it demonstrates how great underreporting is.

The analysis of clinical trials data was reported by the firm to show a statistically significant lower occurrence of violent behavior as defined by the "aggression cluster" of terms among fluoxetine patients compared to placebo. The data for this comparison were derived from spontaneously reported events during clinical trials, not intentionally ascertained. As a result, these data do not permit any conclusion regarding the comparative occurrence of violent behavior.

Discussion

The firm presented a review of eight selected adverse events. Our assessment differs somewhat from the sponsor's in several areas. One comment applicable to the entire submission is that fatal reports were not separately analyzed or described.

For eosinophilia, there are five spontaneous reports of reactions suggestive of eosinophilia-myalgia syndrome in the absence of L-tryptophan use. The firm does not view this as a problem.

For GBS, we believe the existing data raise the possibility that fluoxetine confers an increased risk of occurrence. The firm reached an opposite conclusion but failed to account for underreporting of adverse events. In other situations which have been documented, fewer than 10-20% of fatal or potentially fatal adverse events have been reported. The firm also did not account for the difference between number of persons exposed to a drug and the cumulative person-time of exposure. In the situation of GBS, one must also account for the probable immunologic basis for the disorder. Foreign antigen(s) capable of triggering this reaction typically do so over a shorter rather than longer period of exposure. In the case with fluoxetine, it is possible that a patient on fluoxetine for more than one or two months ceases to be at risk for "drug-induced" GBS. If the majority of patients used the drug for longer periods of

time, the relative risk could be substantially underestimated if the concept of "period at risk" is not adjusted.

For pulmonary reactions, dyspnea is the only symptom in most patients subsequently found or suspected to have immunologically based (hypersensitivity) lung disease. The firm currently recommends discontinuation of fluoxetine if rash appears. We believe dyspnea, as a symptom of possible allergic pulmonary disease is at least as important as rash, but dyspnea is not currently specified as an indication for discontinuation.

The firm's analysis of suicidality does not resolve the issue. The firm acknowledged that its clinical trials were not designed to study this and that the quality and specificity of data to be gleaned from these trials to address suicidality were poor. The data presented in some tables showed higher percentages of suicidality among fluoxetine patients than among tricyclic or placebo patients, but these differences did not reach statistical significance. The discussion of the report by Teicher et al. pointed out the difficult problem of studying this question. However, the firm's strongest argument against the findings of Teicher were those it presented from Fava and Rosenbaum. As shown above, the summary provided by the firm while technically correct did not express the overall appearence of the data. The actual data showed a higher percentage of treatment-emergent suicidality among fluoxetine (2.9%) than tricyclic (0.8%) patients with borderline statistical significance. Interestingly, the proportion of patients with treatment-emergent suicidality on fluoxetine in this study was similar to that reported by Teicher et al.

Because of apparent largescale underreporting, the firm's analysis cannot be considered as proving that fluoxetine and violent behavior are unrelated.

David J. Graham

David J. Graham, MD, MPH

Concur: RVS 9/9, Chief, Epidemiology Branch

cc:
Laughren/Brecher (HFD-120)
Anello (HFD-700)
Stadel/Graham/Rosa/Baum/Wise (HFD-733)
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DRU 1.7 fluoxetine
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