DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-936

SEP 9 1987

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Lilly Reasearch Laboratories
Attention: M. W. Talbott, Ph.D.
Regulatory Affairs
Indianapolis, Indiana 46285

Dear Dr. Talbott:

Please refer to your New Drug Application dated September 6, 1983 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation PROZAC® (fluoxetine hydrochloride) capsules.

Please also refer to your submissions dated

September 6, 1983
December 9, 1983
February 29, 1984
March 29, 1984
June 22, 1984
July 18, 1984
August 14, 1984
August 17, 1984
September 7, 1984
October 2, 1984
October 23, 1984
October 31, 1984
October 31, 1984
December 17, 1984
January 30, 1985
February 7, 1985
February 21, 1985
April 23, 1985
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July 12, 1985
July 18, 1985
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July 30, 1985
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April 2, 1986
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January 27, 1987
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January 30, 1987
February 3, 1987
February 3, 1987
February 5, 1987
February 6, 1987
February 10, 1987
February 19, 1987
February 20, 1987
February 23, 1987
March 12, 1987

EXHIBIT
Thompson 40

Pz 364 2740

03/22 17:36

We have completed our review of the application as submitted with draft labeling. We find the application approvable for the use of fluoxetine in the management of major depressive disorder. We do not find the data and evidence provided sufficient, however, to justify a qualification of the claimed indication regarding the efficacy of the product in the presence of anxiety associated with primary depression. Anxiety symptoms are common in primary depressive disorders, they generally improve as depressive symptoms abate, and they are not known to have any predictive value in regard to clinical response to therapy. Consequently, we consider statements regarding anxiety a meaningless and potentially misleading extension of any approved antidepressant indication. To support specific claims for the use of fluoxetine in treating anxiety symptoms, the efficacy of Prozac in primarily anxious patients would have to be demonstrated.

Final approval of the application will require 1) submission of additional safety related analyses including a brief summary of any new information bearing on the safety of fluoxetine that was accumulated in the interval between October 15, 1986 (the cut-off date for your most recent major safety update) and the date of your receipt of this letter, 2) revision of your proposed labeling as indicated, 3) appropriate and full responses, including data displays and tabulations, requested in notes embedded within the text of the attached draft labeling proposal, 4) your agreement to the conditions described in the section of this letter entitled "Biopharmaceutic Requirements," 5) your commitment to submit within the first year of marketing full reports of the two additional efficacy studies you have conducted that may provide a basis for revising the dosing recommendations made in the proposed product labeling, 6) your commitment, should the two studies described above prove inadequate, to perform additional trials to establish a basis for drafting more precise directions for the use of fluoxetine, 7) your submission of a summary reviewing all actions taken or actions now pending before foreign national drug regulatory agencies involving fluoxetine, 8) your submission of copies of all draft and/or approved foreign labeling (with English translations where necessary), and 9) a review of, and report upon, the archival domestic and foreign literature discussing any findings that identify actual or potential risks associated with the use of fluoxetine. The cut-off date for this review should be as recent as possible and explicitly cited.

1) Additional Safety Analyses and Brief Interim Safety Summary:

a) Additional Analyses:

Although extensive safety evaluations have been performed, we remain concerned about the existence of three putative fluoxetine associated syndromes: 1) a cutaneous-systemic syndrome, 2) a serotonin syndrome, and 3) the "zimeldine-like" syndrome.

Before the marketing of fluoxetine can be permitted, it is important to be certain that we have done all we reasonably can either to establish or to exclude the existence of these syndromes. If we are reasonably certain that a syndrome exists, product labeling must fully describe the syndrome's characteristics and provide proper guidance about management.

The processes we use to assess each putative syndrome must be systematic and must be fully documented in the administrative record. We propose, therefore, that the following procedure be applied to the evaluation of the putative cutaneous-systemic syndrome. An identical strategy should also be applied to the assessment of the 'serotonin' and "zimeldine-like" syndromes.

Further evaluation of the putative 'cutaneous-systemic' syndrome:

Designating rash as the index element of the syndrome, a table, that is, a matrix, should be developed listing the 183 US cases, identified previously by you, who had any form of dermatologic pathology (including urticaria). A row should be assigned to each patient. The columns of the matrix must be sufficient in number to enumerate all types of common ADRs, abnormal physical findings, and abnormal laboratory results reported in close temporal association by any of the 183 patients. In this manner, a table allowing the ready identification of similar patterns of rash associated events will be created.

[Note: If this method of building the table leads to one that becomes too unwieldy, we will be ready to discuss the means with you to make the matrix more manageable.]

In entering events into the table, however, only those occurring concurrently with or in close temporal association to the dermatologic lesion should be enumerated. Obviously, there would be little point in linking a headache at week 3 with a rash that occurred transiently during week 1 of treatment.

In addition to the columns that will depend upon an audit of the actual events reported (e.g., arthralgia, fever, leukocytosis, transaminase elevation, proteinuria, edema, etc.), the matrix should also contain columns for other facts of interest and possible explanatory variables. Specifically, a column should be provided for type of rash, severity of rash, the calender date of onset of the rash, the duration of fluoxetine treatment at the time of onset of the rash, dose at time of the rash, and, critically, the date of full recovery of the patient. If date of recovery is not known, a full report on the patient must be provided. It is particularly important to acknowledge the fact if the final status (physical well being) of the patient with a rash is unknown.

Matrices of identical form and content should be developed for patients who suffered a rash while on active antidepressant treatment or placebo. One matrix should be formed for those on active drug, another for placebo.

Further evaluation of the putative 'Serotonin Syndrome:'

For your evaluation of the 'serotonin' syndrome, we suggest that you use nausea as the index for the tabulation. We picked nausea because it is clearly drug related (its incidence among fluoxetine treated patients is twice that seen among placebo patients) and it is extremely common. Obviously this will lead to the formation of a very large table, but we know of no other way to cull out the more common clusters of symptoms associated with fluoxetine use.

In the case of this table, however, we are less interested in laboratory findings than we are in the possible linkage of nausea to other acutely occurring phenomena and, then, the relationship of these observed clusters to dose, dosing regimen and duration of exposure to fluoxetine.

Using the technique described for the cutaneous systemic matrix would lead to the generation of an impossibly large matrix. It would contain almost 1200 rows and endless columns corresponding to each of the reported ADRs in the entire data base. Thus, we have to find some means to limit the table to patients who experienced acute events concurrently. Unfortunately, until an attempt is actually made to generate a table, we will have little sense of what the limitation will be. Consequently, we propose to work with you iteratively on this analysis. Remember, in this particular case, our purpose is to develop information that will be helpful in drafting improved directions for the use of fluoxetine, directions that will make it more tolerable to patients. Specifically, we wish to determine if single dose size, rather than total daily dose predicts the occurrence of the 'syndrome.' We also wish to determine and document the occurrence of tolerance to its acute dysphoric components.

For example, using the data tabulated, we could examine the incidence of nausea and related phenomena at identical daily doses and dosing regimen across time of exposure to fluoxetine.

Further evaluations to document how a 'zimeldine-like' syndrome was excluded.

We recognize that your original approach to this problem relied upon evaluating the comparative risk of a 'zimeldine' syndrome among fluoxetine and control exposed patients. Unfortunately, this approach does not make clear in the record precisely which patients were identified for purposes of comparison. Consequently, we wish to see a matrix developed for this purpose as well. We suggest that you use 'flu-like' syndrome as the index and generate a table that includes fever, leukocytosis, and weakness among its various columns. It is also critical in this table to make clear if the final status of each patient enumerated is known (e.g., whether it is known that the patient is alive and well).

Common assessment of clusters identified after the matrices are assembled:

Once each matrix is fully prepared, we ask that experienced clinicians on your staff identify what they consider to be common patterns (clusters) of adverse events occurring among the patients enumerated in each table. Your report would explain the rules actually employed to identify clusters and would enumerate, for each matrix, the number of patients among those listed who displayed each identified cluster.

The analysis could stop here, but we would ask that you work with us on performing one additional step. We would like to attempt to estimate what role chance association between independent events (e.g. say headache and insomnia) plays in the generation of any identified cluster. Obviously,

whether or not a cluster is a 'true' syndrome is often decided subjectively on the basis of hunches, intuition and biologic plausibility.

This is not especially reassuring. Indeed, we would prefer it, if a more systematic approach could be taken before a declaration is made that a particular cluster of adverse events/abnormal lab results is linked to the use of a drug. Specifically, we are concerned that in large databases involving the study of thousands of patients chance will lead to the formation of groups of patients exhibiting identical clusters of unrelated adverse events. For example, consider the fluoxetine database of 6000 patients. Headache, insomnia and nausea occur commonly. Most of us would agree that these symptoms could each reflect different manifestations of excess serotonin and be part of a 'serotonin' syndrome, but they might also occur together merely because of chance. To illustrate, assume that each of these events does occur independently of the other two, that is they are not part of a syndrome, then the risk of all three occurring in any one patient is about 0.007 (derived from the product of the independent incidence of each event --0.13 x 0.23 x 0.22--). Using this 'p' for the compound event of nausea, vomiting and headache, the binomial distribution predicts that there is a good chance (about 50%) that 42 patients would be observed with the cluster in a database of 6000 patients.

If you are willing, we would propose to work with our biometric consultants and with you to determine if we can develop a practical and systematic approach to distinguish such apparent syndromes from real ones. (For example, putative clusters might be evaluated using any one of a number of multivariate techniques--logistic regression, cluster analysis, etc.)

b) Brief Interim Safety Analysis

This report is intended to provide the Agency with any new information that might affect a decision on the approvability and/or labeling of Prozac. A summary report similar in format to what was provided in your December 11, 1986 safety update would be acceptable. In addition, we ask that you submit whatever preliminary postmarketing information is available to you regarding the safety experience with Prozac use in Belgium and South Africa.

2) Labeling:

Accompanying this letter (Attachment 1) is the Agency's proposal for the labeling of Prozac. We believe it presents a fair summary of the information available on the benefits and risks of Prozac. In some instances, however, the best means to deal with a particular issue or concern is unclear. Consequently, we require your further cooperation. Thus, embedded within the proposal, set off by brackets, [sic], are specific questions and/or requests related to the given section of the text.

If you have any questions about these requests, division staff will be happy to discuss them in detail. Moreover, we would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

Please provide several copies of proposed final labeling in final printed format. This presentation of labeling will facilitate our final review. In addition, please submit in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Neuropharmacology, and the second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not for proposed materials.

3) Biopharmaceutic Requirements:

a) The application for the 20 mg Pulvule is approvable. However, we ask that you submit, when available, the results of your radiolabeled disposition study 67, and the final report for study 85, a pharmacokinetic study of Prozac in patients with liver dysfunction.

b) Regarding the dissolution methodology and specification of this NDA 18-936:

[redacted]

c) Please forward 300 units of the 20 mg Pulvule to the Chief of Biopharmaceutics Research Branch, HFN-224, FOB-8, Rm 6067, 200 C Street S.W., Washington, D.C. 20204.

4) Clinical Requirements:

The antidepressant efficacy of Prozac was demonstrated in three placebo controlled studies. In two of these studies [Fabre (19) and a multicenter study (27)], patients were administered Prozac on a divided schedule (morning and noon), and were titrated up to 60 mg/day by the end of the first week and up to 80 mg/day for the remainder of these trials. In both studies, a majority of patients were dosed at 80 mg/day for most of their treatment.

The third study demonstrating the efficacy of Prozac (Study 62) involved a comparison of placebo and three fixed doses of Prozac: 20, 40, and 60 mg/day, with the entire dose being given in the morning. Treatment was initiated with the assigned dose (i.e., no titration) and this may have contributed to the high dropout rate in the 60 mg group. This study demonstrated the superiority of the 20 mg Prozac dose over placebo, but was not readily interpretable for the 40 and 60 mg doses because of a greater proportion of dropouts for adverse events in these groups and the higher dropout rate overall for the 60 mg group.

We are aware of two additional fluoxetine efficacy studies you have conducted, based on presentations made at the NCDEU Meeting in May, 1987. One was a dose response study comparing fluoxetine at doses of 5, 20 and 40 mg/day, as well as placebo. This study appears to demonstrate the effectiveness of both the 20 and 40 mg doses, with no advantage for the 40 mg dose (and also suggests some activity even at a 5 mg dose). The second study involved the randomization of patients failing to respond to fluoxetine at 20 mg/day after 3 weeks to either a 20 or 60 mg dose. After 5 additional weeks of treatment, approximately 40% of both groups responded, again with no advantage for the higher dose. On the basis of our preliminary viewing of the data from your two additional studies, we are inclined to call attention to the limitations on our ability to draft precise directions for fluoxetine's use in the Dosage and Administration Section.

Obviously, until we have had a chance to review these studies in detail, we would not be able to offer any firm conclusions about them nor rely on them to draft more definitive directions for fluoxetine's use. Consequently, we ask that you submit full reports on these two additional studies in a timely manner.

5) Report on Actions taken by other National Drug Regulatory Authorities:

We require a review of the status of all fluoxetine actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter.

6) Submission of all Draft and/or Approved Labeling from Foreign Countries:

This is self-explanatory.

7) Submission of a Review of the Archival Literature:

We need to have in hand, prior to approval, a report on the world's archival literature that provides your warrant that you have reviewed it systematically, and in detail, and discovered no finding that would adversely affect conclusions about the safety of fluoxetine. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of

articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described.

Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Conclusion:

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action the FDA may take action to withdraw the application.

This drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions please contact Mr. Tony DeOrco, Consumer Safety Officer at (301) 443-3830.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

PROZAC™
FLUOXETINE HYDROCHLORIDE

DESCRIPTION:

Prozac (fluoxetine hydrochloride, Lilly) is an antidepressant for oral administration; it is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated as (+)-N-methyl-3-phenyl-3-[(alpha,alpha,alpha-trifluoro-p-tolyl)-oxy]-propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$. Its molecular weight is 345.79. A dose of 20 mg is equivalent to 57.8 micromoles. The structural formula is:

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 50 mg/ml in water.

Each Pulvule contains fluoxetine hydrochloride equivalent to 20 mg of fluoxetine. It also contains F D & C Blue No. 1, gelatin, iron oxide, silicone, starch, titanium dioxide, and other inactive ingredients.

CLINICAL PHARMACOLOGY:

Pharmacodynamics:

The antidepressant action of fluoxetine is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies in animals and man suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine. Animal studies have shown that fluoxetine binds to various brain receptors in vitro, but much less potently than do classical tricyclic antidepressants.

[Note to firm: Your proposal to discuss EKG changes in this section of the labeling causes us concern. We fear that your description of the EKG findings in some 700 Prozac treated patients may be misinterpreted by the reader as evidence that Prozac carries no significant cardiovascular risk. Perhaps this so, it may even be likely, but the true test of this will only come after extensive experience is gained with patients who suffer from cardiovascular injury. Certainly, controlled trials of patients with cardiovascular disease can provide useful information that might be presented in this section. For example, a recently published study by Roose, Glassman et. al illustrates a direct approach to evaluation of the comparative risks of antidepressants in patients with carefully defined degrees of cardiovascular impairment. (Roose et al., J. of Clin. Psychopharm. 7:247-251 (1987)).

It is important to acknowledge your right, however, to present these data in labeling. We believe it is much more reasonable to display them in the same subsection where the results of other laboratory tests are presented, the ADR section.]

Absorption, Distribution, Metabolism and Excretion:

[Note to the firm: Please evaluate this section for accuracy and completeness. It has been written on the basis of our understanding of your reports, some of which were preliminary. We acknowledge that we may have misunderstood and/or misinterpreted specific conclusions, and we are fully prepared to revise this section to improve its accuracy and understandability.]

Systemic Bioavailability:

In man, following a single oral 40 mg dose, peak plasma levels of fluoxetine in the range of 11 to 42 ng/ml are observed after six to eight hours.

Food does not appear to affect the systemic bioavailability of fluoxetine, although it may slow the rate of its absorption inconsequentially.

Protein Binding:

Over the concentration range from 200 to 1000 ng/ml, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and alpha-1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been studied, but may be important (See Precautions section).

Metabolism:

Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other, unidentified metabolites. Metabolism is the primary route of elimination. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, norfluoxetine's potency as a serotonin uptake blocker is essentially equivalent to fluoxetine's. Inactive water soluble metabolites of fluoxetine (e.g., glucuronides) are excreted by the kidney, but this appears to be a minor route of elimination

[Note to the firm: We inferred the insignificance of renal excretion from your reports on radiolabeled recovery and glucuronide recovery. Is there any direct evidence, however, about the proportion of any dose actually excreted as a recognizable fluoxetine metabolite via the kidney?]

Clinical Issues Related to Metabolism/Elimination:

The complexity of the metabolism of fluoxetine has several consequences which may potentially affect fluoxetine's clinical use.

Accumulation and Slow Elimination:

The relatively slow elimination of fluoxetine (elimination half-life of 2 to 3 days) and its active metabolite, norfluoxetine (elimination half-life of 8 to 9 days), assures significant accumulation of these active species in chronic use. After 30 days of dosing at 40mg per day, blood levels of fluoxetine in the range of 137 to 302 ng/ml and norfluoxetine in the range of 100 to 220 ng/ml have been observed. Blood levels of fluoxetine were higher than those predicted by single dose studies, presumably because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days.

Thus, even if patients are given a fixed dose for weeks, steady state may not be achieved. Nonetheless, blood levels do not appear to increase without limit. Specifically, patients receiving fluoxetine at doses 40 to 80 mg a day over periods as long as three years did not exhibit, on average, blood levels appreciably different than those seen among patients treated for shorter intervals of time.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks. This is of potential consequence when drug withdrawal is required.

Liver Disease:

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. In a study of cirrhotic patients, the elimination half-life of fluoxetine was found to be substantially longer (8.6 days) than in patients without liver disease; nor-fluoxetine elimination was also delayed, although to a lesser degree. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a low dose should be used. (See Precautions and Dosage and Administration sections).

Renal Disease:

When single doses of fluoxetine were administered to subjects with varying degrees of renal impairment, the disposition of fluoxetine and norfluoxetine was similar in subjects with all levels of impaired renal function, including anephric patients on chronic hemodialysis, although the half-life of fluoxetine did increase somewhat with decreasing renal function. With chronic administration, some accumulation of fluoxetine or its metabolites (possibly including some not yet identified) may be expected in patients with impaired renal function and use of a relatively low dose is advised (See Precautions section).

Age:

The effects of age upon the metabolism of fluoxetine have been incompletely explored. The disposition of single doses of fluoxetine in healthy elderly

subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear dispositition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness.

do we accept this?

INDICATIONS AND USAGE:

Prozac is indicated for the treatment of depression. The efficacy of Prozac was established in five and six week trials with depressed outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder.

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least two weeks); it should include at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of Prozac in hospitalized depressed patients has not been adequately studied.

must we say it this way?

The effectiveness of Prozac in long term use, that is, for more than five to six weeks, has not been systematically evaluated in controlled trials.

again - this is more negative than data warrant

CONTRAINDICATIONS:

None known

[Note to the firm: While it has been traditional to include a generic statement contraindicating the use of a drug in patients "hypersensitive," that is presumably allergic, to the drug, the regulations, 21 CFR 201.57 (d) specifically proscribe this approach unless the evidence shows the risk to be a known problem. Clearly, any physician qualified to administer a drug can be reasonably presumed to understand that it is ordinarily imprudent to administer a drug to a patient who has a past history of responding to it adversely.

Actually, your proposed recommendation takes on considerable importance given fluoxetine's profile of adverse reactions. We note that approximately 4% of patients treated develop a rash. In the absence of a known mechanism, many physicians may presume the rash is mediated by an immunological mechanism, that is that the rash is a manifestation of hypersensitivity to fluoxetine. As your submissions document, however, two-thirds of the patients who developed a fluoxetine associated rash recovered despite continuation of therapy. Even more critical, in the vast majority of patients, rash does not appear to be a very serious event. Do you wish to contraindicate the use of Fluoxetine in any patient

very reasonable

developing a rash? If you do, you should say so explicitly, justifying why such a contraindication is needed. Again, our action is not intended to preclude thoughtful discussion of the problem. The issue of rash and hypersensitivity should be fully discussed, but in the appropriate section of labeling.]

WARNINGS:

The Long Elimination Half-Life of Fluoxetine and its Metabolites:

Because of the long elimination half-lives of the parent drug (2-3 days) and its major active metabolite (7-9 days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. (See Clinical Pharmacology and Dosage and Administration sections).

Cutaneous/Systemic Syndrome:

[N.B.--note to firm: please adjust the number of patients (i.e., underlined below) identified in this section in your draft FPL to reflect the true denominator for patient exposures that might have led to the detection of a rash had one developed. This number should be consistent with the final total supplied in the final Safety Update.]

During premarketing testing involving more than 4000 subjects, approximately four percent of fluoxetine treated patients developed a rash. Among these cases, almost a third were withdrawn from treatment, because of the rash and/or systemic signs or symptoms associated with the rash. Systemic manifestations reported in association with rash include fever, leukocytosis, arthralgias, edema, proteinuria and mild transaminase elevation. Most patients responded promptly to discontinuation and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Whether the association of rash and systemic illness constitutes a true fluoxetine induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury and almost two thirds of those developing a rash continued to take fluoxetine without any consequence. Of note, however, is the fact that two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome, was considered variously to be a vasculitis or erythema multiforme.

[Note to the firm: This warning statement reflects our necessary uncertainty about and sensitivity to the possible significance of any

linkage between lab findings, systemic signs and discontinuations among patients with rash. If you can provide a convincing, data based, enumeration and analysis of the linkage between laboratory test findings, systemic signs, symptoms and rash among patients discontinuing with any cutaneous manifestation to assuage our concerns, we would be open to modification and/or alternative positioning of this statement. [See approvable letter discussion.]

PRECAUTIONS:

General:

Anxiety and Insomnia:

Anxiety, nervousness and insomnia were reported by a substantial number of Prozac treated patients (10 to 15%). These dysphoric symptoms led to drug discontinuation in 5% of Prozac treated patients.

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Altered Appetite and Weight:

Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

A proportion of Prozac treated patients in controlled clinical trials (approximately 9%) experience anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of Prozac treated patients compared to 4% of placebo and 3% of tricyclic antidepressant treated patients. However, only rarely have Prozac patients been discontinued for weight loss.

Activation of Mania/Hypomania:

During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures:

Twelve patients among more than 6000 evaluated in the course of premarketing development of fluoxetine experienced convulsions, a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide:

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness:

Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing.

In patients with cirrhosis of the liver, the clearance of fluoxetine and its active metabolite, norfluoxetine, is decreased, thus increasing the elimination half-lives of these substances. A reduction in starting dose and rate of dose escalation should be considered.

Renal elimination is not a major route of elimination of fluoxetine. However, until adequate numbers of patients with renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference with Cognitive and Motor Performance:

Prozac does not appear to have a prominent sedative effect, and also did not increase the psychomotor impairment associated with ethanol use in a study designed to test that effect. However, any psychoactive drug may impair judgment, thinking or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients:

Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions:

Tryptophan:

Five patients receiving Prozac in combination with tryptophan experienced toxic reactions, including agitation, restlessness and gastrointestinal distress. This finding is consistent with numerous animal studies showing interactions between fluoxetine and 5-hydroxytryptophan (5-HTP).

Monamine Oxidase Inhibitors:

Although no clinical data are available on the effects of the combined use of fluoxetine and MAO inhibitors, it seems prudent to avoid their combined use until their potential for interaction has been studied systematically in controlled clinical trials. Based on experience with the combined administration of MAOI and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Prozac.

Diazepam clearance:

The half-life of concurrently administered diazepam may be prolonged in some patients.

Potential effects of co-administration of drugs highly bound to plasma proteins:

Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein, (e.g., coumadin, digitoxin) may cause a shifts in blood levels potentially resulting in an adverse effect. Conversely, adverse effects may result from the administration of a drug which is tightly bound to protein to a patient taking fluoxetine.

CNS active drugs:

The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy:

There are no clinical data establishing the safety or benefit of the combined use of ECT and fluoxetine.

was it this or 5HTP?

Carcinogenesis, Mutagenesis, Impairment of Fertility:

There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for 2 years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects on the basis of the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately 5 and 9 times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy: Teratogenic Effects:

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses 9 and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers: It is not known whether, and if so, in what amount, this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children: Safety and effectiveness in children have not been studied.

Use in the Elderly:

Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac and no unusual adverse age related phenomena have been identified. A single dose pharmacokinetic study in healthy elderly patients showed no age-related change in elimination patterns, but this is not sufficient to rule out possible differences in prolonged use or in elderly patients with systemic illness.

ADVERSE REACTIONS:

Commonly Observed:

The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo treated patients were: nervous system complaints, including anxiety, nervousness and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea and diarrhea; and dizziness or lightheadedness.

[N.B. Note to the firm: The concept of a "serotonin syndrome," one characterized by agitation, anxiety, insomnia, tremor, nausea, vomiting and headache, is often discussed in association with 5-HT uptake inhibitors. In protocol 62, for example, patients given large single doses of fluoxetine appeared to experience this cluster of symptoms and we have learned from other national drug regulatory authorities that similar clusters of complaints are being reported with marketed drugs that possess serotonin uptake blocking activity. If this is a true syndrome, and we are predisposed to believe that it is, the labeling should draw attention to its existence clearly, especially because the practitioner may be able to minimize its severity (e.g., by using smaller single divided doses of fluoxetine.)

However, we also believe that syndromes should be established on the basis of compelling evidence, not fanciful speculation. As discussed in detail in our approvable letter proper, we believe that some attempt must be made to distinguish between chance association of these phenomena (because they occur commonly) and their linkage in a 'serotonin syndrome.'

If we can agree that the data support the existence of a particular syndrome, either the opening paragraph of this section or, perhaps, the Precautions section, can be revised to reflect its importance. In this regard, if we agree that the syndrome truly exists, sui generis, its course and response to various interventions should be described.]

Associated with Discontinuation of Treatment:

Fifteen percent of approximately 4000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritis.

Incidence in Controlled Clinical Trials:

The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course

of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TREATMENT EMERGENT ADVERSE EXPERIENCE
INCIDENCE IN PLACEBO-CONTROLLED
CLINICAL TRIALS

Body System/ Adverse Event[a]	Percentage of Patients Reporting Event	
	Prozac (n=1730)	Placebo (n=799)
Nervous		
Headache	21.9	17.4
Nervousness	18.3	9.0
Insomnia	13.8	7.4
Drowsiness	11.8	6.3
Anxiety	9.9	5.9
Tremor	8.0	2.4
Dizziness	5.4	3.2
Fatigue	4.2	1.1
Sensation disturbance	1.8	2.1
Sedated	1.8	1.2
Libido, decreased	1.6	--
Lightheadedness	1.7	--
Concentration decreased	1.4	--
Digestive		
Nausea	22.7	10.8
Diarrhea	12.8	7.6
Mouth dryness	10.2	7.0
Anorexia	8.8	1.5
Dyspepsia	6.2	4.4
Constipation	4.6	3.6
Pain, abdominal	3.5	3.1
Vomiting	2.4	1.2
Taste change	1.9	--
Flatulence	1.7	1.4
Gastroenteritis	1.2	1.5
Skin and Appendages		
Sweating, excessive	8.1	4.0
Rash	2.8	1.7
Pruritus	2.5	1.4

[a]Events reported by at least 1% of Prozac patients are included.
--Incidence less than 1%.

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here

TREATMENT EMERGENT ADVERSE EXPERIENCE
INCIDENCE IN PLACEBO-CONTROLLED
CLINICAL TRIALS

Body System/ Adverse Event[a]	Percentage of Patients Reporting Event	
	Prozac (n=1730)	Placebo (n=799)
Body as a Whole		
Asthenia	4.3	1.9
Infection, viral	3.8	3.2
Pain, limb	1.6	1.2
Fever	1.6	--
Allergy	1.4	1.1
Influenza	1.2	1.5
Pain, chest	1.2	1.2
Edema	1.0	--
Respiratory		
Upper respiratory infection	8.3	7.3
Flu-like syndrome	2.9	2.0
Nasal congestion	2.8	2.5
Pharyngitis	2.8	1.5
Headache, sinus	2.4	1.9
Sinusitis	2.1	2.2
Cough	1.7	1.7
Dyspnea	1.4	--
Cardiovascular		
Hot flushes	1.7	1.1
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	1.8	2.4
Pain, joint	1.3	1.1
Pain, muscle	1.3	1.2
Urogenital		
Menstruation, painful	2.1	1.5
Sexual dysfunction	1.8	--
Frequent micturition	1.7	--
Urinary tract infection	1.2	--
Special Senses		
Vision disturbance	2.9	1.7

[a]Events reported by at least 1% of Prozac patients are included.
--Incidence less than 1%.

Other Events Observed During the Premarketing Evaluation of Prozac:

This section reports event frequencies for adverse events occurring in approximately 4000 subjects who took multiple doses of Prozac in US premarketing studies. The conditions and duration of exposure to Prozac varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to Prozac treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the PRECAUTIONS section of the labeling.

The following definitions of frequency are used. Frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: Frequent-abdominal pain, back pain, injury/accident and unspecified pain; infrequent-cyst, face edema, malaise, neck pain, pelvic pain; rare-enlarged abdomen, abscess, chills & fever, hangover effect, hernia, jaw pain, LE syndrome, moniliasis, neck rigidity, serum sickness and ulcer.

Cardiovascular: Frequent-vasodilation; infrequent-angina pectoris, arrhythmia, abnormal electrocardiogram, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; rare-AV block (first degree), bradycardia, bundle branch block, heart block, myocardial infarct, phlebitis, sinus bradycardia, thrombophlebitis, varicose vein, vascular headache.

Digestive: Frequent-increased appetite; infrequent-aphthous stomatitis, colitis, dysphagia, eructation, gastritis, gingivitis, glossitis, hyperchlorhydria, periodontal abscess, thirst, and tongue edema; rare-cholelithiasis, duodenal ulcer, enteritis, esophagitis, fecal incontinence, hepatitis, hepatomegaly, increased salivation, jaundice, liver function tests abnormal, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue discoloration and tooth caries.

Endocrine: Infrequent-hypothyroidism; rare-diabetes mellitus, goiter.

Hemic and Lymphatic: Infrequent-anemia and lymphadenopathy; rare-leukocytosis, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased and thrombocythemia.

Metabolic and Nutritional: Infrequent-gout, peripheral edema, weight loss and weight gain; rare-dehydration, enzymatic abnormality, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal: Frequent-arthralgia, and myalgia; infrequent-arthritis, bone pain, bursitis, myositis and tenosynovitis; rare-osteoporosis and rheumatoid arthritis.

Neoplasia: Rare-breast neoplasm, carcinoma, cervix carcinoma, benign skin neoplasm and thyroid adenoma.

Nervous: Frequent-paresthesia; infrequent-abnormal gait, akathisia, anergy, ataxia, buccocclusal syndrome, CNS stimulation, convulsion, disturbance of memory, hyperkinesia, hypesthesia, incoordination, neuralgia, neuropathy, speech disorder and vertigo; rare-abnormal electroencephalogram, acute brain syndrome, chronic brain syndrome, CNS depression, coma, dystonia, extrapyramidal syndrome, hypertonia, myoclonus, nystagmus, and torticollis.

Psychiatric: Frequent-agitation, depression and abnormal thinking; infrequent-addiction, amnesia, apathy, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hysteria, libido increased, manic reaction, paranoid reaction, and psychosis; rare-neurosis, personality disorder and withdrawal syndrome.

Respiratory: Frequent-rhinitis and sinusitis; infrequent-asthma, bronchitis, epistaxis, hyperventilation, laryngitis, pneumonia, voice alteration and yawn; rare-hemoptysis, hiccup, laryngeal edema and lung fibrosis.

Skin and Appendages: Infrequent-acne, alopecia, contact dermatitis, dry skin, eczema, herpes simplex, maculopapular rash and urticaria; rare-erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, injection site reaction, nail disorder, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, skin fungus, and vesiculobullous rash.

Special Senses: Frequent-taste perversion; infrequent-amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, photophobia and tinnitus; rare-cataract, deafness, diplopia, iritis, ptosis, refraction disorder, strabismus, and taste loss.

Urogenital: Infrequent-abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, proteinuria, urinary retention, urinary urgency, vaginal hemorrhage, and vaginitis; rare-abortion, breast enlargement, dyspareunia, female lactation, hematuria, hypomenorrhea, metrorrhagia, orchitis, polyuria, pyelonephritis, salpingitis, urethral pain, urethritis, urinary incontinence, urolithiasis and vaginal moniliasis.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance Class:

Prozac is not a controlled substance.

Physical and Psychological Dependence:

Prozac has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the premarketing

clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome or 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 Prozac misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE:

Animal Experience:

The oral LD_{50} in rats and mice was found to be 452 and 248 mg/kg, respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Human Experience:

As of mid 1987, there was one death among 33 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. The one death involved a combined overdose with approximately 1800 mg of fluoxetine and an undetermined amount of maprotiline. Blood levels of fluoxetine and maprotiline were 4.57 mcg/ml and 4.18 mcg/ml, respectively. One other patient who reportedly took 3000 mg of fluoxetine experienced two grand mal seizures. The actual amount of drug absorbed may have been less due to vomiting. Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania and other signs of CNS excitation. Except for the one death noted above, all other overdose cases recovered without residua.

Management of Overdose:

Gastric evacuation either by the induction of emesis, lavage, or both should be performed. Following evacuation, activated charcoal may be administered every six hours during the first 24 hours after ingestion. Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures.

There are no specific antidotes for Prozac. Because Prozac has a large volume of distribution, neither diuresis, dialysis, hemoperfusion, or exchange transfusion is likely to be of benefit. The physician should consider contacting a poison control center on the treatment of any overdose.

DOSAGE AND ADMINISTRATION:

Acute treatment:

In controlled trials used to support the efficacy of fluoxetine, patients were treated with 20mg to 80mg a day given in divided doses (morning and noon to avoid insomnia). The importance of dividing the daily dose is documented by the fact that many patients given single doses exceeding 20mg experienced distressing side effects, in some instances leading them to discontinue treatment.

Recent studies, not fully reported at the time of approval of Prozac, suggest that no more than 20mg a day total fluoxetine may be required to obtain a satisfactory antidepressant response.

Thus, until additional studies are performed, it is impossible to identify definitively the best of all possible dosing strategies. One prudent approach, which takes into account the long half-life of fluoxetine's active metabolite, nor-fluoxetine, and which clearly minimizes acute distressing side effects, entails a slow upward titration.

Specifically, using this approach, fluoxetine would be started at a dose of 20mg a day. Even if no immediate clinical improvement were observed, the dose would not be incremented for a period of two weeks.

At two weeks, in the continuing absence of a clinical response, the dose could be incremented.

If more than 20mg a day of fluoxetine is to be administered, a b.i.d. schedule (i.e., morning and noon) should ordinarily be employed.

Although the evidence clearly documents that fluoxetine doses as great as 80mg a day can be given safely, evidence is not available to assess whether a dose of this magnitude is required to achieve and/or maintain antidepressant effect.

As with other antidepressants, the full antidepressant effect may be delayed until four weeks of treatment or longer.

Maintenance/Continuation/Extended treatment:

There is no body of evidence available to answer the question of how long the patient treated with fluoxetine should remain on it. It is generally agreed among expert psychopharmacologists (circa 1987) that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

HOW SUPPLIED:

Pulvules: fluoxetine hydrochloride (equivalent to 20 mg fluoxetine), green and off-white (No. 3105)(100's), NDC 0002-3105-02

Store at controlled room temperature of 59° to 86°F (15° to 30°C).

ANIMAL TOXICOLOGY:

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphophilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.