JFW DEC 10 1986

Weinstein, A. C., Indianapolis

cc: Dr. W. J. Damberg
S. Heymanns
B. v. Kolitz
Dr. H.-J. Weber
Weinstein, C., Indianapolis

Dwyer

Please find enclosed the final version of the package insert (physician's - encl. 1 - and patient's information encl. 2 -). All but 1 change has been discussed and accepted. We additionally included the interactions with tryptophan noted in the paper by Steiner et al.

Please note that in Germany patient's information is distributed with each single package and has to relate to the respective strength only. So, based on the general recommendations in the physician's information following adjustments have been made for the different strengths:

"If not prescribed differently by the physician it is recommended to administer Fluctin once daily, preferably in the morning. Ingestion with food is possible".
(This applies for all strengths)

[illegible] capsule/d is
s. capsule.
In the elderly and patients with less body weight maximum dose should not exceed 3 capsules of Fluctin 20/d.
In patients with severe liver impairment half of the scheduled dose should be given, i.e. 1 capsule every 2nd day up to 2 capsules/d.

FLUCTIN 20
A dose of 1-2 capsules/d is recommended. In patients with severe liver impairment half of the scheduled dose should be given, i.e. capsule every second day up to 1 capsule/d.

2/...

EXHIBIT
H.N. Solee
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mm/fn/21v

Pz2467 204

Fluctin 40
A dose of 1-2 capsules/d is recommended. In the elderly and patients with less body weight maximum dose should not exceed 1 capsule/d. In patients with severe liver impairment half of the scheduled dose should be given, i.e. 1 capsule every second day up to 1 capsule/d.

Fluctin 60
A dose of 1 capsule per day is recommended. In patients with severe liver impairment half of the scheduled dose should be given, i.e. 1 capsule every second day.

We assume your approval unless notified differently till Dec. 15. We apologize for that tough deadline but would run otherwise into troubles with our own timeframe.

Also we send you a translation of our proposed response for the BGA (encl. 3), [redacted] second expert opinion on phospholipidosis (encl. 4) and the documentation on suicide gestures compiled here in Bad Homburg (encl. 5). (The case summaries Dr. Wernicke sent are not attached but will be included, too.) We would appreciate your comments also till Dec. 15.

Regards

for
Dr. H. N. Schulze-Bolce

Encl.

pne/-h/219

Endl. 1

Physician's Information

Fluctin

1. Name of Drug: Fluctin 20/30/40/60

2. Regulations for distribution:

on prescription

This drug contains a substance of which the action is not completely known to the medical science and for which the manufacturer has to submit an experience report to the responsible federal authority according to § 46/6 AMG.

3. Indication group, active components:

antidepressant

Fluctin 20, one capsule contains 22.4 mg fluoxetine hydrochloride equivalent to 20 mg fluoxetine

Fluctin 30, Fluctin 40 etc.

4. Indications:
As in patient's information

5. Contraindications:
As in patient's information (but without precaution statements)

6. Side effects:
Following adverse events have been observed in clinical trials listed according to descending frequency of occurence:
as in patient's information

Weight loss is a frequent observation with Fluctin treatment. Patients with normal weight lost 1 kg on the average during a 6 week treatment period and overweight patients 2 kg.
Occasionelly rash occured, which was very rarely accompanied by arthralgia and fever. In such cases it may become neccessary to discontinue Fluctin and if necessary treat with corticosteroids temporarily.
Depressed leucocyte counts and elevation of serumtransaminases had been observed rarely.

7. Interactions:
Fluctin shall not be coadministered with MAO-inhibitors. MAO-inhibitors shall be discontinued at least 2 weeks before start of treatment with Fluctin. Also the concomitant use of tryptophane shall be avoided.
There are only limited experiences available concerning the concomitant application of electroshock-therapy.
Elimination of diazepam was prolonged in interaction studies in volunteers. Obersrvations suggesting a significance of this effect had not been made in clinical trials.

hns/mb/220

Based on the currently available investigations in volunteers there is no evidence for interactions with alcohol, barbiturates, oral antidiabetics and thiazide-diuretics.

No interactions had been observed in clinical trials when antihypertensives, analgesics, chloralhydrate and benzodiazepics, thyroid-hormones, antihistamines, antibiotics, cimetidine, antacids, or lithium were administered.
Alcohol has to be avoided during treatment although in specific investigations no amplification of the alcohol action by Fluctin had been observed.

8. Warning statements:
None

9. Most important incompatibilities:
None known

10. Dosage:
The dose is 20 - 80 mg fluoxetine per day. Usually treatment with 20 mg fluoxetine per day is sufficient.
Fluctin may be administered once daily preferably in the morning. It may be administered with food.
In severe impairment of liver function plasma clearance of fluoxetine is reduced. Therefore only half of the scheduled dose may have to be administered. This may be done by alternate administration every 2nd day.
Although plasma clearance in the elderly was not different from normal patients in specific investigations, a maximum dose of 3 capsules/day = 60 mg of fluoxetine is recommended in the elderly and patients with low body weight.

11. Kind of application, duration of treatment:
Fluctin is for oral use.
Up to now there are experiences with treatments up to 6 years in single cases.

12. Overdosage, emergencies, symptoms, antidots:
More than 30 cases of overdosage have been reported during clinical trials. In all cases in which Fluctin was the only drug ingested patients survived. The highest dose ingested was approx. 3000 mg. In this case 2 brief seizures were observed. Commonly the clinical symptoms consisted of dizziness, nausea, vomiting, tachycardia, also accomodation disturbances. Severe arrhythmias did not occur.
Primary detoxication on the day of ingestion by gastric lavage may be useful, while diuresis, dialysis or haemoperfusion do not promise to be effective because of the large volume of distribution of Fluctin.

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13. Pharmacology, toxicology:

Pharmacology:

The mechanism of action of fluoxetine as an antidepressant appears to be its inhibition of serotonin reuptake at synaptic nerve terminals.

Animal studies suggest that in contrast to tricyclic antidepressants fluoxetine in therapeutic doses would not inhibit catecholamine reuptake and that there is no direct action on neurotransmitter receptors such as cholinergic, adrenergic, histaminergic or serotonergic and would not have direct effects on the heart. Studies in volunteers revealed no evidence for clinically relevant influence on cortisol, prolactin, HCG, LH, FSH, and testosterone. Heart rate, blood pressure and ECG were not significantly affected in clinical trials.

Fluoxetin is absorbed to at least 95 %. Maximum plasma concentrations occur appr. 6 hours after ingestion. Food delays the rate of absorption but not the extent of absorption. Fluoxetine is metabolised to the largest extent and is eliminated with its metabolites predominantly renally and partially via the bile. The major metabolite is norfluoxetine, formed by demethylation. Norfluoxetine also is a selective serotonine reuptake inhibitor. The half life of fluoxetine after single dose is about 2 days and after multiple dose 4 days. The half life of norfluoxetine is about 7 days after single and multiple dose.

Plasmaconcentrations reach a steady-state after 2 - 3 weeks.

Plasma-clearance in patients is for fluoxetine approx. 20 l/hour and for norfluoxetine approx. 3 l/hour. After cessation of therapy the drug is excreted within 3 - 5 weeks.

Volume of distribution for fluoxetine and norfluoxetine is about 20 - 45 l/kg and plasma protein binding is 94 %.

Elderly and patients with renal impairment including functional anephric patients did not demonstrate significant changes of plasma clearance. In patients with severe impairment of liver function, however, the metabolism of fluoxetine is delayed.

Up to now, there are no data available concerning distribution of fluoxetine in cerebrospinal fluid, breast milk or concerning transplacental diffusion in humans.

Toxicology:

Carcinogenicity, mutagenicity, fertility and teratogenicity studies did not reveal any abnormalities.

Mice, rats, and dogs which had been given fluoxetine for 3 - 12 months showed phospholipid accumulation in lung, liver, adrenal and retina. These changes were all reversible and not characterized by clinical symptoms or other toxic sequelae.

Specific studies in volunteers and patients particularly in comparison to compounds which are known to induce phospholipidosis in humans revealed no findings suggesting similar abnormalities in humans by fluoxetine.

14. Precautions:
There is no indication of any toxic effect of Fluctin on the offspring. However, during pregnancy Fluctin especially during the first 3 months only should be administered if clearly needed.
Patients with severe impairment of liver function showed a delay in metabolism of Fluctin so that an adjustment of dose must be performed (see dosage).
Fluctin does not have sedating properties. In agitated patients or with significant sleep disturbances it is recommended to coadminister sedative medication at the start of treatment with Fluctin.
Manic and psychotic states have been reported in single cases in susceptible patients.
Until the antidepressive effect occurs particular severe depressive patients and patients with suicidal risk have to be observed sufficiently.
According to currently available investigations no impairment is to be expected while operating machines and driving cars however, it is recommended to observe carefully the individual reaction.
According to today's common clinical practice liver specific enzyme concentrations and haemotologiced parameters should be determined in regular intervals particularly in longterm treatment.

15. Stability:
After expiry date Fluctin shall not be administered.

16. Recommendations for storage:
None. Fluctin may be stored with room temperature.

17. Pharmaceutical formulations and package sizes:
Fluctin 20, Fluctin 30, Fluctin 40, Fluctin 60

18. Date of information:
December 1986

19. Company:
Eli Lilly GmbH
Teichweg 3
D-6300 Gießen

Encl. 2

PATIENT'S INFORMATION

Eli Lilly GmbH Gießen

Fluctin 20
Active component: Fluoxetine Hydrochloride

Composition: 1 capsule contains 22.4 mg fluoxetine hydrochloride equivalent to 20 mg fluoxetine

Indication:
Fluctin is indicated for the treatment of depressive syndromes of different origin as for example endogenous, neurotic and reactive depressions.

Contraindications:
Hypersensitivity to fluoxetine.
Treatment of children and adolescents up to 18 years with Fluctin is not recommended since no clinical experiences are available for this group of age.
Fluctin should not be administered to nursing mothers.

Precaution:
There is no indication of toxic influence on the offspring. However, Fluctin only should be administered during pregnancy particularly during the first three months when careful benefit risk assessment has been made by the physician.
In patients with severe impairment of liver function, the metabolism of Fluctin is prolonged, so that adjustment of dose has to be performed (see dosage).

Side Effects:
The following side effects may occur: nausea, headache, nervousness, sleeplessness, anxiety, drowsiness, diarrhea, dry mouth, tremor, sweating, anorexia, dizziness, dyspepsia, constipation, asthenia, disturbance of vision, vomiting, sedation, pruritus. Many of these events are symptoms of depression and most of them subside during course of treatment.

Slight weight loss is a frequent event occuring with treatment of Fluctin.
Occasionally rush may occur which very rarely is accompanied by arthralgia and fever. In these cases Fluctin shall not be continued and the treating physician shall be consulted.
Decrease of white blood count or elevation of liver enzymes were rarely observed.

Precaution:
Fluctin lacks sedating effects. In agitated patients or patients suffering from significant sleep disturbances, additional application of a sedative is recommended at beginning of the treatment. Until antidepressive actions become effective, patients are to be observed sufficiently.

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According to currently available investigations no impact is to expect on operating machines and driving cars. However, it is recommended to observe the individual reaction carefully.

Interactions:
Fluctin shall not be administered concomitantly with MAO-inhibitors. MAO-inhibitors have to be discontinued at least two weeks before treatment with Fluctin is initiated. A concomitant therapy with tryptophan should also not be performed.
Elimination of diazepam may be slightly prolonged.
Up to now no interactions have been observed with concomitant administration of barbiturates or other sedating and sleeping agents, oral antidiabetics, thiazide-diuretics, antihypertensives, analgesics, thyreoid-hormones, antihistamines, antibiotics, cimetidine and other gastric acid inhibiting drugs or lithium. Alcohol is to avoid during treatment although in specific investigations no amplification of the action of alcohol was observed.

Dosage and usage:
If not prescribed differently by the physician it is recommended to administer Fluctin once daily, preferably in the morning. Ingestion with food is possible.
The dose is 1 to 4 capsules FLUCTIN 20 per day. Usually, treatment with one capsule/day FLUCTIN 20 is sufficient. In the elderly and patients with less body weight the dose should not exceed 3 capsules FLUCTIN 20 per day. In patients with severe impairment of liver function the dose should be halved, that means 1 capsule every second day to 2 capsules per day.

After expiry date Fluctin shall not be administered.

Drugs have to be stored inaccessible for children.

hms/mb/219

PATIENT'S INFORMATION

Eli Lilly GmbH Gießen

Fluctin 30
Active component: Fluoxetine Hydrochloride

Composition: 1 capsule contains 33.6 mg fluoxetine hydrochloride equivalent to 30 mg fluoxetine

Indication:
Fluctin is indicated for the treatment of depressive syndromes of different origin as for example endogenous, neurotic and reactive depressions.

Contraindications:
Hypersensitivity to fluoxetine.
Treatment of children and adolescents up to 18 years with Fluctin is not recommended since no clinical experiences are available for this group of age.
Fluctin should not be administered to nursing mothers.

Precaution:
There is no indication of toxic influence on the offspring. However, Fluctin only should be administered during pregnancy particularly during the first three months when careful benefit risk assessment has been made by the physician.
In patients with severe impairment of liver function, the metabolism of Fluctin is prolonged, so that adjustment of dose has to be performed (see dosage).

Side Effects:
The following side effects may occur: nausea, headache, nervousness, sleeplessness, anxiety, drowsiness, diarrhea, dry mouth, tremor, sweating, anorexia, dizziness, dyspepsia, constipation, asthenia, disturbance of vision, vomiting, sedation, pruritus. Many of these events are symptoms of depression and most of them subside during course of treatment.

Slight weight loss is a frequent event occuring with treatment of Fluctin.
Occasionally rush may occur which very rarely is accompanied by arthralgia and fever. In these cases Fluctin shall not be continued and the treating physician shall be consulted.
Decrease of white blood count or elevation of liver enzymes were rarely observed.

Precaution:
Fluctin lacks sedating effects. In agitated patients or patients suffering from significant sleep disturbances, additional application of a sedative is recommended at beginning of the treatment. Until antidepressive actions become effective, patients are to be observed sufficiently.

hns/mb/219

According to currently available investigations no impact is to expect on operating machines and driving cars. However, it is recommended to observe the individual reaction carefully.

Interactions:
Fluctin shall not be administered concomitantly with MAO-inhibitors. MAO-inhibitors have to be discontinued at least two weeks before treatment with Fluctin is initiated. A concomitant therapy with tryptophan should also not be performed.
Elimination of diazepam may be slightly prolonged.
Up to now no interactions have been observed with concomitant administration of barbiturates or other sedating and sleeping agents, oral antidiabetics, thiazide-diuretics, antihypertensives, analgesics, thyreoid-hormones, antihistamines, antibiotics, cimetidine and other gastric acid inhibiting drugs or lithium. Alcohol is to avoid during treatment although in specific investigations no amplification of the action of alcohol was observed.

Dosage and usage:
If not prescribed differently by the physician it is recommended to administer Fluctin once daily, preferably in the morning.
Ingestion with food is possible.
The dose is 1 to 2 capsules FLUCTIN 30 per day. In patients with severe impairment of liver function the dose should be halved, that means 1 capsule every second day to 1 capsule per day.

After expiry date Fluctin shall not be administered.

Drugs have to be stored inaccessible for children.

hma/mb/219

PATIENT'S INFORMATION

Eli Lilly GmbH Gießen

Fluctin 40
Active component: Fluoxetine Hydrochloride

Composition: 1 capsule contains 44.8 mg fluoxetine hydrochloride equivalent to 40 mg fluoxetine

Indication:
Fluctin is indicated for the treatment of depressive syndromes of different origin as for example endogenous, neurotic and reactive depressions.

Contraindications:
Hypersensitivity to fluoxetine.
Treatment of children and adolescents up to 18 years with Fluctin is not recommended since no clinical experiences are available for this group of age.
Fluctin should not be administered to nursing mothers.

Precaution:
There is no indication of toxic influence on the offspring. However, Fluctin only should be administered during pregnancy particularly during the first three months when careful benefit risk assessment has been made by the physician.
In patients with severe impairment of liver function, the metabolism of Fluctin is prolonged, so that adjustment of dose has to be performed (see dosage).

Side Effects:
The following side effects may occur: nausea, headache, nervousness, sleeplessness, anxiety, drowsiness, diarrhea, dry mouth, tremor, sweating, anorexia, dizziness, dyspepsia, constipation, asthenia, disturbance of vision, vomiting, sedation, pruritus. Many of these events are symptoms of depression and most of them subside during course of treatment.

Slight weight loss is a frequent event occuring with treatment of Fluctin.
Occasionally rush may occur which very rarely is accompanied by arthralgia and fever. In these cases Fluctin shall not be continued and the treating physician shall be consulted.
Decrease of white blood count or elevation of liver enzymes were rarely observed.

Precaution:
Fluctin lacks sedating effects. In agitated patients or patients suffering from significant sleep disturbances, additional application of a sedative is recommended at beginning of the treatment. Until antidepressive actions become effective, patients are to be observed sufficiently.

hns/mb/219

According to currently available investigations no impact is to expect on operating machines and driving cars. However, it is recommanded to observe the individual reaction carefully.

Interactions:
Fluctin shall not be administered concomitantly with MAO-inhibitors. MAO-inhibitors have to be discontinued at least two weeks before treatment with Fluctin is initiated. A concomitant therapy with tryptophan should also not be performed.
Elimination of diazepam may be slightly prolonged.
Up to now no interactions have been observed with concomitant administration of barbiturates or other sedating and sleeping agents, oral antidiabetics, thiazide-diuretics, antihypertensives, analgesics, thyreoid-hormones, antihistamines, antibiotics, cimetidine and other gastric acid inhibiting drugs or lithium. Alcohol is to avoid during treatment although in specific investigations no amplification of the action of alcohol was observed.

Dosage and usage:
If not prescribed differently by the physician it is recommended to administer Fluctin once daily, preferably in the morning. Ingestion with food is possible.
The dose is 1 to 2 capsules FLUCTIN 40 per day. In the elderly and patients with less body weight the dose should not exceed 1 capsule FLUCTIN 40 per day. In patients with severe impairment of liver function the dose should be halved, that means 1 capsule every second day to 1 capsule every day.

After expiry date Fluctin shall not be administered.

Drugs have to be stored inaccessible for children.

PATIENT'S INFORMATION

Eli Lilly GmbH Giessen

Fluctin 60
Active component: Fluoxetine Hydrochloride

Composition: 1 capsule contains 67.2 mg fluoxetine hydrochloride equivalent to 60 mg fluoxetine

Indication:
Fluctin is indicated for the treatment of depressive syndromes of different origin as for example endogenous, neurotic and reactive depressions.

Contraindications:
Hypersensitivity to fluoxetine.
Treatment of children and adolescents up to 18 years with Fluctin is not recommended since no clinical experiences are available for this group of age.
Fluctin should not be administered to nursing mothers.

Precaution:
There is no indication of toxic influence on the offspring. However, Fluctin only should be administered during pregnancy particularly during the first three months when careful benefit risk assessment has been made by the physician.
In patients with severe impairment of liver function, the metabolism of Fluctin is prolonged, so that adjustment of dose has to be performed (see Dosage).

Side Effects:
The following side effects may occur: nausea, headache, nervousness, sleeplessness, anxiety, drowsiness, diarrhea, dry mouth, tremor, sweating, anorexia, dizziness, dyspepsia, constipation, asthenia, disturbance of vision, vomiting, sedation, pruritus. Many of these events are symptoms of depression and most of them subside during course of treatment.

Slight weight loss is a frequent event occuring with treatment of Fluctin.
Occasionally rush may occur which very rarely is accompanied by arthralgia and fever. In these cases Fluctin shall not be continued and the treating physician shall be consulted.
Decrease of white blood count or elevation of liver enzymes were rarely observed.

Precaution:
Fluctin lacks sedating effects. In agitated patients or patients suffering from significant sleep disturbances, additional application of a sedative is recommended at beginning of the treatment. Until antidepressive actions become effective, patients are to be observed sufficiently.

hns/mb/219

According to currently available investigations no impact is to expect on operating machines and driving cars. However, it is recommended to observe the individual reaction carefully.

Interactions:
Fluctin shall not be administered concomitantly with MAO-inhibitors. MAO-inhibitors have to be discontinued at least two weeks before treatment with Fluctin is initiated. A concomitant therapy with tryptophan should also not be performed.
Elimination of diazepam may be slightly prolonged.
Up to now no interactions have been observed with concomitant administration of barbiturates or other sedating and sleeping agents, oral antidiabetics, thiazide-diuretics, antihypertensives, analgesics, thyreoid-hormones, antihistamines, antibiotics, cimetidine and other gastric acid inhibiting drugs or lithium. Alcohol is to avoid during treatment although in specific investigations no amplification of the action of alcohol was observed.

Dosage and usage:
If not prescribed differently by the physician it is recommended to administer Fluctin once daily, preferably in the morning. Ingestion with food is possible.
The dose is 1 capsule FLUCTIN 60 per day. In patients with severe impairment of liver function the dose should be halved, that means 1 capsule every second day.

After expiry date Fluctin shall not be administered.

Drugs have to be stored inaccessible for children.

hns/mb/219

Anx. 5

Translation of our answer letter to the BGA

Dear ladies and gentlemen,

In reply to your letter of Feb. 26, 1985 we would like to inform you of the following: after careful consideration of the arguments brought forward as well as of the benefit and the potential risks of the preparation we cannot share the opinion that registration should be rejected. Reasons for a rejection are not applicable.

Re.: 1.
It is not true that the therapeutic efficacy of fluoxetine has not been sufficiently proved.

Re.: 1.1
Two expert opinions, written in 1985 on the basis of the data also submitted to you at that time, are concluding that the efficacy of fluoxetine has been established and that the profile of action has been sufficiently characterized. ([redacted], attachment 2) [redacted], attachment 1).

An expert opinion of Aug. 31, 1986 written for the application for registration in the U.K. also considers the efficacy as established ([redacted], attachment 3).

The methodical criticism (classification of the depressions in the inclusion criteria, wash-out phase, concomitant treatment with other psychotropic agents, selection of control preparations) seems to us incomprehensible after our extensive comments of October 1984. This opinion is also expressed in the expert opinions by [redacted] and [redacted] and is thoroughly discussed there.

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A reanalysis of the results of study protocol 27 already submitted where only the patients were considered who were administered fluoxetine or the control substance respectively without additional psychotropic therapy (analysis of Apr. 03, 1985; volume 55, p. 00-121) shows no essential difference compared to the evaluation of Aug. 14, 1984 (volume 49, p. 1-172) where all patients with or without psychotropic concomitant medication were included.

Meanwhile the results of clinical trials in Germany are available confirming the transferability of the principal statements of the American data (attachments 4, 5, 7, 16, 17). In these studies we used the ICD classifications of depression preferred in this country and we followed your suggestion to use amitriptyline as control substance in both the big multicenter projects ([redacted] study I in out-patients; study II in hospital in-patients).

Experience in treating hospital in-patients has been broadened and is comparable to experience made with out-patients ([redacted] attachment 5 and report no. 56, volume 51, p. ; [redacted] attachment 7 and report no. 58, volume 51, p. ; [redacted] attachment 6 and report no. 57, volume 51, p. ; [redacted] attachment 4 and report no. 55, volume 51, p. 1).

Re.: 1.2
Controlled clinical trials versus comparator drugs over a period of more then 6 months are uncommon. There are also ethical objections as well as technically organisational problems in carrying them out.

Safety data are generally presented in open studies especially when they exceed a period of 6 months.

3/...

[redacted] as well as [redacted] judged in their expert opinions the data presented already in 1984 as being sufficient.

Meanwhile these data have also been published. The authors have come to the conclusion that fluoxetine is safe and effective in long-term therapy (attachment 15).

A further analysis including a comparison of adverse event clusters in short-term and in long-term administration is presented in the FDA safety update of June 1986 (attachment 14, report no. 62, volume 54). Based on this evaluation Montgomery too concludes (attachment 3) that fluoxetine is effective and well tolerated in long-term therapy.

So far, there are no reports on development of dependence.

Re.: 2
We see no suspicion of unjustifiable adverse effects in fluoxetine.

Re.: 2.1
The updated summary of all suicidal actions worldwide (deadline Aug. 31, 1986) amounts to 62 in the fluoxetine therapy group and in the total of the control groups there are 15 cases (attachment 11).

6903 patients were treated with fluoxetine and in the control group there were 2310 patients. According to this the incidence rate for fluoxetine results in 0,009 and for the control group in 0,0065. The difference is not significant.

This incidence is considerably below the frequency reported for depressive populations [redacted] attachment 13).

4/...

The analysis of the time of occurrance in the individual cases shows that suicidal actions occur neither mainly in the initial phase nor can they be attributed to plasma concentrations increasing to the steady state. Instead they are distributed over the entire duration of exposure up to events following 3 years of long-term administration (attachment 11, table 9). This indicates a genesis immanent the illness rather than induced by the substance. It is therefore justified to relate the reported suicidal actions to the duration of exposure in the individual therapy groups. For fluoxetine the therapy duration is 1168 and for the control groups it is 352 patient years. The incidence rates of 0,054 for fluoxetine and of 0,043 for the control groups. This difference is also not significant.

The analysis (attachment 11) shows - according to the principle of chance - different rates in the smaller observation units of the individual countries. Thus in German studies only one suicide attempt was observed. It occurred in the multicenter study with hospital in-patients and occurred under amitriptyline. All data quoted refer to reports generated according to the "event system" which were initially globally classified as suicidal actions. The analysis of the individual cases shows that for some the description "suicide attempts" is questionable (documentation on suicidal acitons, summary of cases, attachment 11).

Time and again it is brought forward that the initially strongly sedating effect of the tricyclic antidepressant drugs amitriptyline and imipramine possess an effect protecting from suicide and that substances lacking initial sedation or those which even bring about stimulation are subject to the risk of activating patients prior to onset of the antidepressive effect and that therefore suicidal actions may occur more frequently.

5/...

We have paid special attention to this objection and have asked experts for their judgement.

According to [redacted] even the initially submitted data do not indicate that suicidal actions might have to be attributed to the specific effect of fluoxetine. The anyway not very high number of suicidal actions would result from the dynamics of the illness (attachment 13). [redacted] has subjected the initially submitted cases of suicidal actions to intensive casuistic working-up and found no criteria for a drug specific dimension of influence (attachment 17).

On the basis of these evaluations and the actual numbers of the occurrance of suicidal actions we see no cause for the suspicion of a suicidal risk specifically caused by fluoxetine. However, we are making allowances for the requests of the agency by having included the following statement into our product information:

> Fluoxetine does not produce a sedating effect. For patients suffering from agitations or from distinct sleep disturbances additional administration of a sedating or sleep promoting medication is recommended at the beginning of the fluctin therapy.
>
> Up to the onset of the antidepressive effect especially severely ill patients and patients with the risk of attempting suicide ought to be placed under sufficient observation.

Re.: 2.2
In a repeated review of the data we could not find confirmation for the assumption that under therapy with the product an increase of some of the symptoms of the underlying illness, anxiety, sleeplessness and agitation may occur. The reanalyses of Aug. 14, 1984 (volume 49, p. 1-172) and of Apr. 03,

2/...

1985 (volume 55, p. 00-121) demonstrate that some patients are clearly showing signs of agitation possibly induced by the product. Others, however, are showing signs of sedation. This, by the way, is also the case with imipramine.

In addition, we are referring to the expert opinion of [redacted] item 13, p. 24 as well as p. [redacted] (attachment 1).

Re.: 2.3
According to the request of the agency we commissioned a special evaluation (internal medicine) of the findings of pulmonary changes as well as of the results on phospholipid inclusions in the animal experiments and their relevance for humans [redacted] attachment 9).

In the presented findings on the lung the expert can see no indication for a potential phospholipidosis and no risk with clinical relevance for the application in humans.

Meanwhile further investigations were carried out in order to clarify the question to what extent the observations on induction of phospholipidosis in animal experiments are significant for humans.

There are substances in clinical use which cause phospholipid inclusions in the animal experiment which however, from previous experience do not show these findings in humans (e.g. imipramine). Furthermore, there are substances in use which induce phospholipidosis in the application in animals and in humans likewise (e.g. amiodarone).

37 patients who were treated with fluoxetine between 6 months and 6.5 years were compared with a negative control group of about equal size and with a group under imipramine and with a further group under amiodarone therapy. The tests that were

carried out included mainly the lung, the eyes and the peripherial nervous system and were laid out as specifically as possible in order to detect changes possibly caused by phospholipidosis. The data obtained do not indicate a potential occurrance of phospholipidosis in humans (special test for long-term safety of fluoxetine, attachment 8 and report no. 61, volume 53 p. 299-324).

On the total of the findings in the animal experiment and in the application in humans, including these results a new expert opinion was obtained (Hoestler, attachment 10).

[redacted] concludes that fluoxetine at a dose of 20 to 80 mg/day can safely be used in humans.

[redacted] too has again expressed his opinion on the basis of the new results of the investigations (attachment 9).

In the product information we are referring to the findings of the animal experiments.

Reference to item a-c of your letter

We are providing separate information for the physician and the pharmacist and the patient respectively according to the requirements of the "Zweites AMG-Änderungsgesetz" (second law concerning changes of the drug law).

The text of these sets of information is enclosed. Compared with the package insert in the original application for registration, several sections have been revised and adjusted to the changed state of knowledge.

8/...

a) The effect of fluoxetine cannot be termed hepatotoxic. The incidence of liver-enzyme elevation is rather to be called low. There are no severe organ damages [redacted] p. 12/13, attachment 9; [redacted] p. 28, attachment 1; [redacted] p. 5/6, attachment 2).

Relevant transaminase elevations occurred in clinical studies more seldom in the fluoxetine groups than in the active control groups (Report No. 62, Vol. 54, p. 423-424).

An investigation to determine the pharmacokinetics in impaired liver function was done in patients with liver cirrhosis (see attachment 14, p. ...).

As expected, the plasma half-life is prolonged. We therefore recommend to use half the usual dose.

b) According to our opinion no hepatotoxicity exists and the incidence as well as the extent of clinically relevant liver enzyme elevations has to be called low according to general clinical experience [redacted] attachment 9; [redacted] attachment 1) and also in direct comparison with control substances during clinical trials (report no. 62, p. 423-424, Vol. 54). For this reason, we consider the following wording to be appropriate:

> According to the present clinical standard liver specific enzyme concentrations and hematological laboratory parameters should be determined in regular intervals, especially in long-term application.

c) 585 fluoxetine patients had at least two eye examinations in the course of clinical trials. The percentage of the observed changes was below the percentage of all control groups, apart form placebo.

No uniform disorder was detected.

The additional investigations from the study mentioned above regarding phospholipidosis under fluoxetine gave no evidence of changes which appear to be specific, substance related and/or relevant. On this basis the suggestion proposed by the agency can in our opinion be dispensed with.

34 reports are attached to our letter. They include two analyses of pooled data and the results of 7 studies from Germany, further study results from the U.K. and the U.S.A. which were either carried out since the end of 1984 or which were available since then.

With the application for registration of March 2, 1984, and the answer to the letter of concerns of Oct. 19, 1984, further study reports as well as numerous analyses of pooled data were submitted.

Enclosed you will find a tabulation of all available clinical reports arranged according to topics and with references to the individual report numbers (attachment 1B). An evaluating summary of the clinical/pharmacological investigations is presented in the expert opinion by Dr. Lucas of Oct. 08, 1986 (attachment 3) and of the clinical data in the expert opinion by Prof. [redacted] of Aug. 31, 1986 (attachment 3).

10/...

Should you still - in spite of the data and expert opinions now presented - have reservations regarding a positive benefit/risk relation of fluoxetine, then we would like to ask you to grant us the opportunity for an oral hearing before a final decision will be made.

Best regards,

Dr. K. J. Bamberg
Manager Medical Administration

Dr. med. M. N. Schulze-Solce
Deputy Medical Director

Encl.: Volumes 50 - 58 (4 copies)

BVK/BEU/1815

Encl. 4

Translation

Letter to Dr. Schulze-Solce of Dec. 4, 1986
from Prof. [redacted]

Dear Dr. Schulze-Solce,

on request of your company, I have handed in an expert opinion on May 20, 1985, referring to your substance fluoxetine. It is mainly concerned with the problems of adverse events of fluoxetine.

Meanwhile you supplied me with new investigational material which has been produced in the U.S.A. This investigational material which is very clearly documented was carefully examined and reviewed by me and I would like to point out that the questions raised in my expert opinion of May 20, 1985, could be widely cleared by these investigations. Especially the expert opinion by Dr. [redacted] has convinced me completely also in the final conclusions, also with reference to the clinical significance of the inclusion bodies in the lymphocytes.

According to the investigations now available it is my opinion that there is no cause for concern with regard to eye function, nerves and lymphocytes as well as lung function. The investigation presented seems to have been carried out in an especially diligent and correct manner. Here, especially the comparison with the other drugs imipramine and amiodarone appears to be extremely valuable.

Best regards,

(signed) [redacted]

BVW/BEU/1815

hns/mst/296-1

Encl. 5

Documentation on suicide gestures in clinical trials with fluoxetine
(cut off date August 31, 1986)

All suicide gestures reported in fluoxetine trials worldwide have been compiled in this documentation.

For this purpose all events classified as suicide, suicide attempt or drug overdose have been listed for all countries where fluoxetine studies had been ongoing during the time covered by this report.

Adverse events occurring in clinical trials are captured continuously and filed immediately on their receipt. Thus it was possible to include suicide gestures reported from still ongoing studies.

In table 2 - 8 all suicide gestures are listed for each country where it is also stated how many of these were completed suicides and how many had been suicide attempts. All tables list the events for fluoxetine and 'other'. 'Other' represents the control group and includes placebo, active comparator or no drug. This accounts for why sometimes despite the event is listed for fluoxetine derive from controlled studies vs. active drug and placebo as well as from uncontrolled trials.

There have been reports of suicide gestures although no drug was actually given. This is due to the fact that investigators had been instructed to report all observations related to trial patients even after completion of the protocol. So sometimes follow up information for weeks or even months was available and documented. In such cases the suicide gestures are listed with fluoxetine if the event occurred [redacted] days after the withdrawal of the drug (e.g. [redacted]). However they are listed with the control group if they occurred 5 weeks or more after withdrawal of fluoxetine.

In order to calculate incidence rates the total number of patients treated and time of exposure in patient years is given for fluoxetine and the control group in all tables. For all ongoing studies which are still blinded one half of the number already enrolled has been counted for fluoxetine and the other half for the control group.

Table 1 shows the total numbers worldwide for patients and patient years, all suicide gestures, successful suicides and suicide attempts which result from the data of the single countries given in table 2 - 8. The incidence rates per patient and per patient years respectively are given for suicide gestures, suicides and suicide attempts separately.

For all suicide gestures the time since start of treatment is given in table 9. Data for 3 cases for which exact date were not available prior to completion of this analysis.

Table 10 identifies the patients in whom suicide gestures had been reported. A brief summary of all cases mentioned is given subsequently.

If the worldwide numbers are considered the incidence rate is 0.009 (95 % confidence limits: 0.006 - 0.012). This is 1.38 times more than in the control group (p = 0.1627, Fisher's exact test, one tailed). It is 16 times less than in a depressive population. (If according to Pohlmeier, Ref. 50/13, 15 % for the depressives are assumed).

Looking at the different countries the majority of the data has been collected in the USA and Canada. In this group suicide gestures occur 1.16 times less with fluoxetine than in the control group.

In Germany there was only one event reported which occurred on amitriptyline.

In France 17 of 18 suicide gestures had been reported during a 6 months uncontrolled treatment with fluoxetine. The incidence rate is about 10 times nigher compared to US data reflecting a different group of patients and kinc of follow up.

Table 9 illustrates that suicide gestures occur at all points in time during the treatment. There is no relation to a specific period and with respect to fluoxetine pharmacokinetics there is no dose response relationship.

All suicidal gestures included in this compilation have been recorded according to the event system. That means that any observation whether regarded drug related or not was entered into the system. Considering the single case summaries it is doubtful if e.g. patients [redacted] and [redacted] did take fluoxetine at all. Patient [redacted] took an overdose of fluoxetine however she had not been on fluoxetine prior to that so that she had an event on fluoxetine but not in the sense of this evaluation. Patients [redacted] and [redacted] obviously demonstrated no suicidal intent. So if these patients are excluded the incidence rate in this group drops from 0.043 to 0.024.

It is unlikely that patients [redacted] and HC45[redacted] from the US committed suicide gestures as well. Also patient HC4[redacted] was treated after the event for additional 12 months without any difficulty. Further 7 patients could be regarded as not appropriate for inclusion. (See comments given with the respective case summaries.)

Excluding these 13 patients and relating to the time of exposure the incidence rates are 0.043 for both fluoxetine and control group.

Excluding also the 17 cases from the French uncontrolled study and relating to the respective time of exposure (1166 total worldwide patient years - 161.8 = 1006.2 patient years) the incidence rate is 0.033.

It is difficult to compare these data of different kind and sources as if obtained from a controlled trial. However no matter if the best or the worst approach is chosen, there is no evidence for an increased risk of suicide gestures by fluoxetine.

Dr. H. K. Schulze-Solce

Enclosures:

Tables 1 - 10
Case summaries

Bad Homburg, December 8, 1986

Table 1: Suicide gestures (Suizidhandlungen)

Worldwide total

	Fluoxetine	Other*
patient number	6903	2370
patient years	1168	352
suicide gestures total (Suizidhandlungen)	62	15
suicide gestures/pat. no.	0.009	0.0065
suicide gestures/pat. years	0.054	0.043
successful suicides	9	3
succ. suic./pat. no.	0.0013	0.0013
succ. suic./pat. years	0.0077	0.0085
suicide attempts	54	12
suic. att./pat. no	0.0078	0.0052
suic. att./pat. years	0.046	0.034

* Placebo, no drug, comparator

If 1 attempt of a still blinded ongoing study from Finland (see table 6) is added to fluoxetine the ratios are.

gestures/pat. no.	0.0083
gestures/pat. years	0.055

If added to other:

gestures/pat. no.	0.0069
gestures/pat. years	0.045

Table 2: Suicide gestures (Suizidhandlungen)

	USA/Canada	
	Fluoxetine	Other*
patient number	547[illegible]	156[illegible]
patient years	869	25[illegible]
suicide gestures total (Suizidhandlungen)	3[illegible]	10
suicide gestures/pat. no.	0.005[illegible]	0.0064
suicide gestures/pat. years	0.035	0.039
successful suicides	4	1
succ. suic./pat. no.	0.0007[illegible]	0.00064
succ. suic./pat. years	0.004[illegible]	0.0039
suicide attempts	26	9
suic. att./pat. no.	0.0047	0.0058
suic. att./pat. years	0.03	0.035

* Placebo, no drug, comparator

Table 3: Suicide gestures (Suizidhandlungen)

Germany

	Fluoxetine	Others*
patient number	142	133
patient years	11.7	11.2
suicide gestures total (Suizidhandlungen)	0	1
suicide gestures/pat. no.	0	0.0076
suicide gestures/pat. years	0	0.09
successful suicides	0	0
succ. suic./pat. no.	0	0
succ. suic./pat. years	0	0
suicide attempts	0	1
suic. att./pat. no.	0	0.0076
suic. att./pat. years	0	0.09

* Placebo, no drug, comparator

Table 4: Suicide gestures (Suizidhandlungen)

	UK, Basingstoke	
	Fluoxetine	Other*
patient number	206	227
patient years	16.7	16.7
suicide gestures total (Suizidhandlungen)	9	3
suicide gestures/pat. no.	0.043	0.013
suicide gestures/pat. years	0.54	0.18
successful suicides	0	1
succ. suic./pat. no.	0	0.0044
succ. suic./pat. years	0	0.053
suicide attempts	9	2
suic. att./pat. no.	0.043	0.0088
suic. att./pat. years	0.54	0.107

* Placebo, no drug, comparator

Table 5: Suicide gestures (Suizidhandlungen)

UK, Erl Wood

	Fluoxetine	Other*
patient number	365	106
patient years	45.5	10.7
suicide gestures total (Suizidhandlungen)	5	1
suicide gestures/pat. no.	0.014	0.009
suicide gestures/pat. years	0.11	0.10
successful suicides	2	1
succ. suic./pat. no.	0.005	0.009
succ. suic./pat. years	0.04	0.10
suicide attempts	3	0
suic. att./pat. no.	0.008	0
suic. att./pat. years	0.07	0

* Placebo, no drug, comparator

Table 6: Suicide gestures (Suizidhandlungen)

	France	
	Fluoxetine	Other*
patient number	451	92
patient years	201.6	46
suicide gestures total (Suizidhandlungen)	18	0
suicide gestures/pat. no.	0.04	0
suicide gestures/pat. years	0.09	0
successful suicides	2	0
succ. suic./pat. no.	0.0044	0
succ. suic./pat. years	0.01	0
suicide attempts	16	0
suic. att./pat. no.	0.035	0
suic. att./pat. years	0.08	0

* Placebo, no drug, comparator

Table 7: Suicide gestures (Suizidhandlungen)

Sweden

	Fluoxetine	Other*
patient number	16	1
patient years	1.6	0.1
suicide gestures total (Suizidhandlungen)	1	0
suicide gestures/pat. no.	0.06	0
suicide gestures/pat. years	0.6	0
successful suicides	1	0
succ. suic./pat. no.	0.06	0
succ. suic./pat. years	0.6	0
suicide attempts	0	0
suic. att./pat. no.	0	0
suic. att./pat. years	0	0

* Placebo, no drug, comparator

Table 8: Suicide gestures (Suizidhandlungen)

Spain, Switzerland, Italy, Belgium, Netherlands, Finland

	Fluoxetine	Other*
patient number	245	190
patient years	21[illegible]	16[illegible]
suicide gestures total (Suizidhandlungen)	0	0
/ pat. no.	0	0
/ pat. years	0	0

* Placebo, no drug, comparator

1 attempt in Finland in an ongoing study, which still is blinded.

Table 9: Occurence of events in time

Fluoxetine treatment duration at point in time of occurence of event (weeks)	Number of events reported (N = 60)
0.5	1
1	4
1.5	4
2	6
3	4
4	4
5	5
6	2
7	1
8	2
9	3
10	2
11	1
12	2
13 - 52	10
53 - 104 (1 - 2 years)	2
105 - 208 (3 - 4 years)	2

Table 10: Suicide gestures/patient identification

Fluoxetine	Other*
USA/Canada	
HCAE [redacted]	HCAE
HCAE	HCAF
HCAF	HCAF
HCAF	HCAF
HCAF	
HCAF	These 16 cases had been evaluated by [redacted] in detail (see enclosed expert opinion, volume 50) and had been already submitted with the initial submission in 1984.
HCAF	
HCAG	
HCAH	
HCAJ	
HCAJ	
HCCD [redacted]	HCCD
HCCD	HCAG
HCCD	HCCJ
HCCD	HCCJ
HCCD	HCDL
HCCN	HCDM
HCDL	
HCAF	
HCDM	
HCAG	
HCDL	
HCAH	
HCAO	
HCDL	
HCDL	
HCCJ	
HCDL	
HCCP	
Germany	BIYSE [redacted] Patient No. [redacted]

* placebo, no drug, comparator

Table 10 (continued): Suicide gestures/patient identification

Fluoxetine	Other
U.K./Basingstoke	
= B1Y/BP/HC	[redacted]
= B1Y/BP/HC	
= B1Y/BP/HC	
= B1Y/BP/HC	
= B1Y/BP/HC	
= B1Y/BP/HC	
= B1Y/BP/HC	
= B1Y/BP/HC	
U.K./Erl Wood	
= B1Y/	[redacted]
= B1Y/	
= HCC	
= B1Y/	
= B1Y/	
= B1Y/	
France	
= B1Y/FP/	[redacted]
=	
= B1Y/FP/0701	
= B1Y/FP/	
= B1Y/FP/	
= B1Y/FP/	
=	
= B1Y/FP/	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
= B1Y/FP/0701	
Sweden	
[redacted]	

HNS/MH/1252-B

Project B1Y SB [redacted]

[redacted] Fluoxetine vs. Amitriptyline, In-Patient Study

Patient No. [redacted]

Case Summary (unblinded, Amitriptyline):

A 64 years old female patient suffering from enc[illegible]sion (ICD 296.1) of retarded subtype was enrolled on 07/03/85 into the study. On entry, her total Hamilton Score was 24 out of 17 items. Suicidality was rated 4. On 08/04/85, she took two capsules b.i.d. of study medication according to protocol. In the evening of the same day, she scratched her wrists and her neck. The surface wounds were treated by a surgeon. After being back in the psychiatric department, she tried to strangle herself with a stocking in the same night at 1.00 a.m. of the following day. She was given benzodiazepines parenterally. Study was discontinued.

This case was unblinded by [illegible] personnel, however, not reported on FD 1639 when it revealed that the comparator was involved. The investigator is still blinded in this case.

FLUOXETINE OVERDOSE

GF. No.: B1Y-BP-HC21, Patient [redacted]

DES/DEN No.: [redacted]

[redacted] Study.

This 63 year old male caucasian entered the study on 18.10.84 with an initial Hamilton score of 24. Having been given his study medication the patient was discharged home, only to be found dead at home a few days later. His medication pack was untouched so he had not taken any study drug. The coroner's report suggested that the cause of death was a overdose of approximately 20 tablets of Chlorethiazole in conjunction with alcohol.

COMPARATOR DRUG OVERDOSE

GPT No.: B1Y-BP-HC24, Patient [redacted]

DLI/DDI No.: [redacted]

[redacted] Study.

This 24 year old female [illegible] with an initial Hamilton score of 22, was admitted to the study on 26.3.86. She continued in the study for 34 weeks at which point she took an overdose of 16 x 1 mg Mianserin. At this point her Hamilton score had reduced to 25. She was not considered to be suicidal and in fact, continued to the end of the study when her Hamilton score was still 29.

COMPARATOR DRUG SUICIDE

GPT No.: B1Y-BP-HC26, Patient [redacted]

DBS/DEM No.: [redacted]

[redacted] Study.

This 58 year old male caucasian with an initial Hamilton score of 24, was admitted on 17.4.86. After 3 weeks in the study the patient was found to have comitted suicide and post mortem examination revealed that he had died of an overdose of Amitriptyline.

FLUOXETINE OVERDOSE

GPT No.: B1Y-BP-HC32, Patient [redacted]

DES/DD: No:: [redacted]

[redacted] (GP) Study.

This 39 year old male caucasian with an initial Hamilton score of 33, was admitted to the study on 2.4.86. He progressed through the study for 5 weeks at which point he took an overdose of 20 x 20 mg capsules of Fluoxetine. He was observed in hospital but recovered spontaneously. He was clearly still depressed at the end of the study with a Hamilton score of 29 but it is not clear whether he had true suicidal intent.

FLUOXETINE OVERDOSE

GPT No.: B1Y-BF-HC24, Patient [redacted]

DBS/DSI No: [redacted]

[redacted] Study.

This 20 years old male caucasian with an initial Hamilton score of 26, was admitted on 10.7.86 and progressed with the study for 3 weeks. At that point his Hamilton score had, in fact, increased to 31. Prior to his next visit he took an overdose of 16 x 20 mg capsules of Fluoxetine which was believed to be a serious suicide attempt. He suffered no adverse experience as a result of his overdose.

FLUOXETINE OVERDOSE

GPT No.: B1Y-BP-MC24, Patient [redacted]

IRL/DEN No.: [redacted]

[redacted] Study.

This 21 year old male caucasian was admitted to the study on 11.9.85 with a Hamilton score on admission of 32 (17 items). At the end of his second week in the study, his Hamilton score had increased to 35 but he admitted to not having taken the proper amount of capsules. He was persuaded to stay in the study but half way through the following week he took an overdose of 15 x 20 mg Fluoxetine capsules. This was seen as a serious suicide attempt but he suffered no apparent adverse events from his overdose.

FLUOXETINE OVERDOSE

GPT No.: B1Y-BP-HC23, Patient [redacted]

DDS/DEN No.: [redacted]

[redacted] (geriatric) Study.

This 71 year old female caucasian was admitted to the study on 6.11.84 with an initial Hamilton score of 24. By the time she returned for her first follow-up visit it was clear that her husband had discouraged her from taking any trial medication and she had become subsequently more depressed to the point where she had taken an overdose of Temazepam and possibly some Fluoxetine. She recovered without any adverse events.

FLUOXETINE STUDY

GPT No.: B1Y-BP-HC26, Patient [redacted]

DES/DEN No.: [redacted]

[redacted] Study.

This 61 year old female caucasian was admitted to the study on 14.1.86 with a Hamilton score of 27. She continued through the study for 3 weeks, at which point she took an overdose of Temazepam and was admitted to hospital though she suffered no adverse events. It was subsequently found that she had not complied with the proper regime of Fluoxetine because her medication pack contained many more capsules than should have been present. Her final Hamilton score was 34.

FLUOXETINE OVERDOSE

GPT No.: B1Y-BP-HC26, Patient [redacted]

DIS/DEN No.: [redacted]

[redacted] Study.

This 41 year old male caucasian with an initial Hamilton score of 28, was admitted to the study on 3.4.85. After 4 weeks in the study his Hamilton score had increased to 27 and he took 7 x 10 mg Temazepam and 4 x 50 mg Trazodone. This was not regarded as serious suicidal intent but he was, in fact, removed from the study at the next visit because of lack of efficacy.

FLUOXETINE OVERDOSE

DES/DEN No.: [redacted]

Previously [redacted] study.

This 23 year old female patient took part in a Fluoxetine trial in 1984 (B1Y-BP-HC50) and her participation in the study had finished during that year. She was however admitted to hospital on 7.6.86 having taken 50 x 20 mg capsules of Fluoxetine which she apparently stored for 2 years. It is difficult to know whether there was any suicidal intent because she discharged herself from hospital the following day having apparently recovered fully.

FLUOXETINE OVERDOSE

GPT No.: BIY-BP-HC22, Patient [redacted]

DEL/DEC No.: [redacted]

[redacted] Study.

This 47 year old patient was admitted to the study on 22.8.84 with an inital Hamilton score of 31. When he returned at the end of 3 weeks of treatment he reported that he had taken 8 capsules of Fluoxetine on one day and 6 capsules on another day of the previous week, without any suicidal intent or adverse experiences. At his next visit he was recorded as having taken again, 8 capsules on one day of the previous week which apparently caused him to develop an itchy rash. There was no apparent suicidal intent from this overdose.

FLUOXETINE OVERDOSE

GFT No.: B1Y-BP-HC22, Patient [redacted]

DLE/DE: No.: [redacted]

[redacted] Study.

This 19 year old female caucasian with an initial Hamilton score of 27 was admitted to the study on 29.5.85. She made good progress during the 6 week trial and her final Hamilton score was 5. However, one week before terminating the study she was said to have attempted an overdose of Lorazepam. She denied any suicidal attempt and was discharged from the study feeling quite well.

[redacted] - B1Y/[redacted]

Case Summary

A 37 years old male outpatient had received 40 mg of fluoxetine for two weeks when he took an overdose of paracetamol and was admitted to hospital. He recovered uneventful. It was felt to terminate the study after further two weeks because of non-return at proper intervals for assessment due to hospital admission, due to overdose of paracetamol.

[redacted] - B1Y/[redacted]

Case Summary

A 20 years old female had received fluoxetine for four months when she took 3000 mg of fluoxetine and 4400 mg of aspirine. Two grand mal fits, lasting 3 and 2 minutes respectively occured. Eventually the patient recovered fully.

It was documented on previous visits by the investigator that the patient was extremely anxious about possible side effects because she had a friend who had had side effects on zimelidine and that she "chopped" and changed medication on her own accord.

[redacted] - B1Y/[redacted]

Case Summary

A 20 years old female outpatient took a multiple drug overdose (? 480 mg fluoxetine, 500 mg paracetamol, ? mg tiriton ?) after 3 weeks on fluoxetine. Restlessness, agitation and tachycardia of 110/min were recorded on hospital admission 1 hour after overdose. She recovered uneventful. Fluoxetine was restarted after 3 days and study was terminated 10 days later according to protocol.

Patient [redacted] (B1Y-[redacted])

This was a 38-year-old male who committed suicide after he had been treated with 60 mg/day of fluoxetine for nine months. Apparently, he took an overdose of Clobazam, amitriptyline and pentazocine. Containers for these drugs were found near the body. No fluoxetine containers were found. The patient could not have taken more than 480 mg of fluoxetine unless he failed to comply with prescribed therapy and was hoarding drug. It was estimated that the patient died four days before the body was found, thus it was not possible to determine levels of drugs. A FD1639 was filed, Mfr. Control No. 84080619A.

UK/Erl Wood

Patient [redacted] (81Y-[redacted]
This was a 67-year-old male who committed suicide by hanging after he had been treated with placebo for 35 days in the UK geriatric depression dose ranging study. A FD1639 was filed, Mfr. Control No. B4060021A.

Patient [redacted] (81Y-[redacted]
This was a 67-year-old male who committed suicide by hanging after having taken 40 mg/day of fluoxetine for five days in the UK fluoxetine vs. amitriptyline adult depression dose ranging study. A FD1639 was filed, Mfr. Control No. B5020600A.

France

84 [redacted] 185 [redacted]

Fluoxetine was started on August 29th, 84. Patient was receiving 60 mg on follow-up visit of September 11th, 84.

Tolerance was very good but anxiety was severe and the next day she attempted suicide.

Two hours after drug intake, the physician observed : "coma vigil", tetanized aspect, impossible to test reflexes, nystagmus of both eyes. Patient was hospitalized, forced urinary output was instituted and patient woke up 6 hours after drug intake.

Because patient failed to show any of the expected symptoms for fluoxetine overdose such as vomiting and nausea, emergency ward physicians were wondering wether patient did indeed take an overdose of fluoxetine. Presenting clinical condition could also be interpreted as an anxiolytic hysterical episode. However all the remaining capsules were missing from the bottle given the day before (i.e. 17 capsules).

Fluoxetine was continued until a second intentional overdose occurred on december 84.

Patient was hospitalized. She confessed several months later that she had taken only a few chlorazepate tablets but no "green capsules" (fluoxetine).

86 [redacted]

Female 37 years old. Good improvement with fluoxetine after eight weeks of treatment. Because of her husband's alcoholic relapse she committed suicide by ingestion of barbiturate and she died.

86 [redacted]

Male 35 years old. Patient slowly improved by fluoxetine treatment. No side effect. During the 6th month of treatment, patient took intentionally 20 fluoxetine capsules after a disagreeable episode with beer and whisky. A light excitation was noted. Fluoxetine was not discontinued.

85 [redacted]

Female 35 years old. Patient improved by fluoxetine but agressivity and hypochondriac complaints increased. After six weeks of treatment, she tried to commit suicide because of problems with her husband and her children. She wanted to be hospitalized again to solve these problems. At that time fluoxetine was not discontinued but now this patient is lost to follow-up.

[redacted] (86 [redacted])

Female - 39 years old.
Well improved during the index episode.
During the first month in the prophylactic phase (fluoxetine or placebo) she experienced again suicide thoughts and tried to commit suicide by overdose.

[redacted] (86 [redacted])

Female - 32 years old.
Good improvement with fluoxetine during the index episode.
This patient relapsed after four months of blinded treatment in the prophylactic phase.
She entered the relapse phase (fluoxetine) and tried to commit suicide after six weeks of treatment in this phase by ingestion of 15 capsules of tercodyn. Fluoxetine was discontinued.

[redacted] (85 [redacted])
85 [redacted]

Female - 37 years old.
During the second week of treatment, this patient tried to commit suicide by ingestion of clorazepate, alcohol and fluoxetine because of a quarrel with a neighbour.
She was hospitalized one night in an intensive care unit. She recovered. Fluoxetine was not discontinued.
At the 6th month of treatment, she tried again to commit suicide because of problems with her husband and her children : ingestion of fluoxetine + clorazepate. She recovered.

[redacted]

Male 69 years old.
Light improvement with Fluoxetine during the 6 months index period.
In the prophylaxis phase (blinded - Fluoxetine vs Placebo) he tried to commit suicide.
He has been hospitalized and Fluoxetine was discontinued. He recovered.

[redacted], M.D.

[redacted]

Female 62 years old.
Good improvement. During the sixth month of treatment, she suddenly tried to commit suicide by ingestion of bleaching water. She recovered and Fluoxetine was stopped.

[redacted] M.D.

[redacted]

Female 40 years old.
Reactive depressive relapse after six weeks of treatment because her boyfriend left her. She tried to commit a suicide by ingestion of benzodiazepines. She recovered and Fluoxetine was discontinued.

[redacted] M.D.

[redacted]

Male, 53 years old.
No improvement. After 12 weeks of treatment, the patient committed suicide with barbiturates and alcohol.
Fluoxetine was discontinued.

[redacted] M.D.

[redacted]

Anxiety and nervousness developed after 24 hours of therapy and insomnia within the next two days. On day 9 of therapy, fluoxetine was stopped because of a suicide attempt with use of benzodiazepines requiring patient hospitalization. Physician thinks suicide attempt may be due to increased anxiety in relation with fluoxetine therapy.

[redacted] M.D.

[redacted]

After 6 weeks of treatment, patient was wary of injections and stopped taking Fluoxetine. When he came back he tried to commit suicide by ingestion of several drugs. He recovered.

[redacted] M.D.

[redacted]

Female 27 years old.
Because of sentimental problems and professionnal difficulties, this patient experienced psychopathic rantus and tried to commit [redacted] Hospitalization. Fluoxetine was discontinued in spite of normal recovery the day after.

[redacted] M.D.

[redacted]

For intentional overdose, patient took 800 mg fluoxetine plus benzodiazepine and possibly phenobarbital. Patient had stage IV coma and recovery was rapid

[redacted] M.D

[redacted] (85 00 [redacted]
Female - 35 years old. Hysterical personality.
Although she was very well improved on the depressive point of view, she still had sentimental problems and she tried to commit suicide. She recovered. Fluoxetine was discontinued.

[redacted]

Patient had depressive episodes of unipolar manic depressive psychosis. Patient committed suicide by [illegible] on 11.00 [illegible] which was the day of his follow-up visit [illegible] to his family. Patient has been very anxious and nervous for the last [illegible] his suicide are that he had been unable to talk him into [illegible] the doctor before the scheduled visit. Patient had also [illegible] suicide attempts [illegible] previously (inhalation of [illegible]). First attempt was in 1971. 82 Patient had been hospitalized in a psychiatric ward several times.

[redacted] M.D.

Sweden

Patient [redacted]
This was a 53-year-old male who was enrolled in a fluoxetine study in Sweden. He committed suicide by hanging after he had been on 60 mg of fluoxetine for 10 days. A FD2035 was filed, Mfr. Control No. [redacted]50900834.