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May 10, 1991

Paul D. Leber, M.D., Director
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Drug Products (HFN-120, Room 10B-45)
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
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RE: NDA 20-031
AROPAX®(paroxetine hydrochloride) Tablets

Dear Doctor Leber:

We are submitting in triplicate our response to Dr. Martin Brecher's request that we provide an analysis of the paroxetine clinical trials database for the occurrence of suicides, suicide attempts, and suicide ideation. One copy is a desk copy for Dr. Brecher.

An analysis of the paroxetine NDA database has been conducted focusing on completed suicides, suicide attempts, and suicide ideation. The results of this analysis are presented and discussed in the enclosed report [Attachment 1] entitled, "Suicidal Ideation and Behavior: An Analysis of the Paroxetine Worldwide Clinical Database".

To summarize in brief, this analysis of data from prospective clinical trials in depressed patients clearly demonstrates that patients randomized to paroxetine therapy were at no greater risk for suicidal ideation or behavior than patients who were randomized to placebo or other active medication.

If there are any questions please contact me at (215) 832-3710.

Yours truly,

Thomas E. Donnelly, Jr., Ph.D.
Director, Regulatory Affairs





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ATTACHMENT 1

[redacted]

PAR000898164

# SUICIDAL IDEATION AND BEHAVIOR:

# AN ANALYSIS OF THE PAROXETINE WORLDWIDE CLINICAL DATABASE

April 29, 1991

CONFIDENTIAL

INTRODUCTION

Suicidal ideation is a universally recognized accompaniment to the symptom complex of depression and, when acted upon by the patient, is the ultimate expression of the illness. Suicide ranks eighth among all causes of death in the United States[1] and accounts for about 15% of deaths in patients with mood disorders[2,3].

A number of studies have suggested that suicidal behavior is linked to central serotonergic dysfunction.[4-6] Low levels of CSF 5HIAA - the primary metabolite of serotonin, have been correlated with suicidality in a subgroup of depressed patients with suicidal intent, but not in a control group of depressed, non-suicidal patients.[7-9] Post mortem studies have revealed that suicide victims possess increased numbers of $5HT_2$ receptors in the frontal cortex, possibly as compensation for decreased availability of serotonin[10-11]. These data provide a rationale for the use of selective serotonin re-uptake inhibitors (SSRIs) in the treatment of depression and extensive literature attests to their efficacy in depression therapy.[12-15]

Case reports have appeared in the literature that describe the development of suicidal ideation in six depressed patients who were undergoing therapy with fluoxetine[16]. However, a recent retrospective study reported finding no significant differences in the intensity, severity or emergence of suicidal ideation between patients treated with fluoxetine and other antidepressant therapies[17]. Suicidal ideation has also been reported in depressed patients taking tricyclic antidepressants (desipramine)[18] and tetracyclic antidepressants (maprotiline)[19].

To explore whether any relationship exists between paroxetine therapy and suicidality, a review of the paroxetine worldwide database has been conducted, using data which were submitted at the time of the New Drug Application for paroxetine. This review focuses on:

1. Suicides (Section 1.0)
2. Suicide attempts (including overdoses) (Section 2.0)

3. Suicidal ideation in the context of:

   a. Reports as adverse events. (Section 3.0).

   b. The suicide items of the Hamilton Depression Rating Scale (HAMD) and the Montgomery Asberg Depression Rating Scale (MADRS). (Sections 4.0 - 4.6).

   c. The Anger/Hostility subcluster of the Hopkins' Symptom Checklist (SCL-56) (Section 4.7).

STATISTICAL METHODOLOGY

Short term data, based on the first 6 weeks of therapy of all worldwide studies, were considered for the analysis of efficacy. All data from worldwide studies, irrespective of time on therapy, were considered for the analysis of safety and the reporting of adverse experiences. Rather than introducing any selection bias, the data from all trials has been pooled.

While patients have been included on an "intent-to-treat" basis, some sample sizes may vary due to the availability of data for any particular parameter which is being assessed. It should be noted that although the pooling of data from different studies provides an overall average, the results may not be homogeneous among all studies due to differences in trial designs.

Mean differences from baseline have been compared using Wilcoxon rank sum tests unless stated otherwise. Frequency tables were compared using either chi-squared or Fisher's Exact test depending on cell size. Resulting p-values are tabulated to provide a relative frame of reference for comparison.

## 1.0 SUICIDES

Data were available for 4,668 patients who were randomized to paroxetine (n=2963), placebo (n=554) and other active treatment regimens (n=1151). Ten suicides were committed by patients who had participated in the worldwide paroxetine clinical trials. Five suicides were committed by patients who were randomized to paroxetine, 2 were committed by patients randomized to placebo, and 3 were committed by patients randomized to other active control regimens.

Of the five suicides committed by patients randomized to paroxetine, 2 patients died of overdose (by a drug other than paroxetine), 2 patients hanged themselves and 1 patient drowned. The time on therapy at which point these individuals took their lives was 10, 45, 47, 144 and 182 days.

Of the two suicides committed by patients "randomized" to placebo, the method by which they took their lives was unknown. Although these patients were actually participating in an active control study, the acts of suicide were committed during participation in the placebo "run-in" phase. The specific points in times at which these individuals took their lives were 2 days (-2) and 7 days (-7) prior to the baseline evaluation.

Of the three suicides committed by patients randomized to active control regimens, 1 patient had been treated with clomipramine, 1 with amitriptyline and 1 with imipramine. The patient treated with imipramine committed suicide by shooting. The method by which the patient who had been treated with amitriptyline took his life was unknown. The time on therapy at which point these individuals took their lives was 18 and 74 days and an unspecified point in time beyond week 7 (>day 49).

The number and incidence of suicidal acts are summarized in Table 1. The incidence is expressed as cases per patient exposure year (P.E.Y.) where total P.E.Y.s is equal to the sum of the duration of treatment for each patient (in days), divided by 365. A patient listing may be found in Appendix 1.

Table 1
Suicides

| | Paroxetine n=2963 1008 P.E.Y. | Placebo n=554 72 P.E.Y. | Active Controls n=1151 218 P.E.Y. |
|---|---|---|---|
| No. (%) | 5 (0.17) | 2 (0.36) | 3 (0.26) |
| No./P.E.Y. | 0.005 | 0.028 | 0.014 |

There were no substantive differences in the number or incidence of suicides among treatment groups.

## 2.0 ATTEMPTED SUICIDES

The incidence of all attempted suicides in patients participating in the worldwide paroxetine clinical trials is displayed in Table 2. The incidence of attempted suicides by overdose, is displayed in Table 3. A patient listing for those who attempted suicide by overdose while randomized to paroxetine is provided in Appendix 2. A patient listing for those who attempted suicide by methods other than overdose while randomized to paroxetine is provided in Appendix 3.

*Table 2*
Attempted Suicides

| | Paroxetine n=2963 1008 P.E.Y. | Placebo n=554 72 P.E.Y. | Active Controls n=1151 218 P.E.Y. |
|---|---|---|---|
| No. (%) | 40 (1.3) | 6 (1.1) | 12 (1.0) |
| No./P.E.Y. | 0.040 | 0.083 | 0.055 |

No substantive differences in the number or incidence of attempted suicides were found among the paroxetine, placebo and active control groups.

*Table 3*
Attempted Suicides by Overdose

| | Paroxetine n=2963 1008 P.E.Y. | Placebo n=554 72 P.E.Y. | Active Controls n=1151 218 P.E.Y. |
|---|---|---|---|
| No. (%) | 28 (0.9) | 3 (0.5) | 8 (0.7) |
| No./P.E.Y. | 0.028 | 0.042 | 0.037 |

No substantive differences in the number or incidence of attempted suicides by overdose were found among the paroxetine, placebo and active control groups.

2.1 Suicide attempts by overdose in patients randomized to paroxetine.

Twenty-eight patients who had received paroxetine therapy attempted suicide by overdose. Nine of the 28 cases involved the ingestion of paroxetine alone, at the following dosages: 2 at 40 mg, 60 mg, 120 mg, 150-200 mg, 360 mg, 420 mg, 850 mg and one unknown quantity. In five of these nine cases, the patients were hospitalized. One patient was administered activated charcoal in an attempt to adsorb the overdose. No abnormal laboratory parameters, vital signs or chest X-rays were reported. ECG data were normal, however, one patient was reported to have sinus tachycardia. Two other patients reported adverse events: dilated pupils, dry mouth, nausea, vomiting and headache. Either no action was taken or few details are available with regard to the other patients who were not hospitalized.

Six patients took overdoses involving paroxetine in combination with other substances: lorazepam, paracetamol, dihydrocodeine, alcohol, nitrazepam, hexobarbitol and placebo tablets. Four of the six patients were hospitalized and one of the four patients was treated by stomach lavage. No abnormal laboratory parameters, vital signs or adverse events were reported. Two patients who were not hospitalized reported adverse events: feeling bloated, nausea, decreased appetite, dizziness, dry mouth, difficulty concentrating, akathesia, blurred vision, excitement and irritability.

Thirteen patients took overdoses; either of medication other than paroxetine, or alcohol.

All of the patients noted above made a full recovery from their overdose experience.

2.2 Suicide attempts other than by overdose in patients randomized to paroxetine.

Twelve patients who had received paroxetine therapy attempted suicide by methods other than by overdose. The following methods were reported, with the number of patients in parentheses: lacerations (5), poisoning (1), defenestration (4), hanging (1) and method unknown (1).

## 3.0 SUICIDALITY REPORTED AS AN ADVERSE EVENT

Adverse events were recorded in all paroxetine clinical trials, whether they were spontaneously reported or elicited from the patient. The worldwide data base was searched for the following investigator (i.e. verbatim) terms:

| | |
|---|---|
| Suicidal ideation | Parasuicidal tendency |
| Suicide risk | Felt suicidal |
| Ideas of suicide | Became suicidal |
| Suicidal thoughts | Suicidal feelings |
| Suicidal tendency | Suicidal threats |

The incidence of suicidality as an adverse event for patients treated with paroxetine, placebo or active control is presented in Table 4.

*Table 4*

Frequency of Suicidality Reported as an Adverse Event

| | Paroxetine n=2963 1008 P.E.Y. | Placebo n=554 72 P.E.Y. | Active Controls n=1151 218 P.E.Y. |
|---|---|---|---|
| No. (%) | 13 (0.4) | 2 (0.4) | 5 (0.4) |
| No./P.E.Y. | 0.013 | 0.028 | 0.023 |

Suicidality reported as an adverse event occurred with similar incidence in each of the treatment groups.

## 4.0 HAMILTON DEPRESSION SCALE SUICIDE ITEM

The Hamilton Depression Scale (HAMD) and the Montgomery Asberg Depression Rating Scale (MADRS) were employed as psychometric instruments in paroxetine clinical trials. Suicidal ideation is assessed by Item #3 of the HAMD and is rated as follows:

0 = absent
1 = feels life not worth living
2 = wishes themselves dead, or any thoughts of possible death to self
3 = suicide ideas or gesture
4 = suicide attempt

Suicidal thoughts are assessed on a 7 point scale in Item #10 of the MADRS, which are anchored as follows:

0 = Enjoys life or takes it as it comes.
1 -
2 = Weary of life. Only fleeting suicidal thoughts.
3 -
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5 -
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

### 4.1 HAMD Suicide Item - Baseline scores

Scores on the HAMD suicide item across treatment groups at baseline are displayed in Table 5. The active control group contains patients who received amitriptyline, imipramine, clomipramine, mianserin, doxepin and maprotiline.

*Table 5*
Baseline Score on HAMD Suicide Item

| HAMD item score | Paroxetine n=2852 | Placebo n=554 | Active Controls n=1101 |
|---|---|---|---|
| 0 | 725 (25.4%) | 127 (22.9%) | 321 (29.2%) |
| 1 | 972 (34.1%) | 212 (38.3%) | 375 (34.1%) |
| 2 | 871 (30.5%) | 186 (33.6%) | 289 (26.2%) |
| 3 | 240 ( 8.4%) | 29 ( 5.2%) | 98 ( 8.9%) |
| 4 | 44 ( 1.5%) | 0 ( 0% ) | 18 ( 1.6%) |

Based on the Hamilton Depression Scale, only 22.9% - 29.2% of patients were without suicidal thoughts prior to treatment.

## 4.2 MADRS Suicide Item - Baseline Scores

The Montgomery Asberg Depression Rating Scale was administered only to patients participating in U.S. studies, accounting for the smaller sample sizes.

Scores on the MADRS suicide item across treatment groups at baseline are displayed in Table 6. The active control group contains patients who received amitriptyline, imipramine and doxepin.

*Table 6*
Baseline Score on MADRS Suicide Item

| MADRS item score | Paroxetine n=1510 | Placebo n=459 | Active Controls n=454 |
|---|---|---|---|
| 0 | 170 (11.3%) | 56 (12.2%) | 54 (11.9%) |
| 1 | 384 (25.4%) | 106 (23.1%) | 124 (27.3%) |
| 2 | 596 (39.5%) | 184 (40.1%) | 175 (38.5%) |
| 3 | 258 (17.1%) | 92 (20.0%) | 74 (16.3%) |
| 4 | 98 ( 6.5%) | 20 ( 4.4%) | 25 ( 5.6%) |
| 5 | 4 ( 0.3%) | 1 ( 0.2%) | 2 ( 0.4%) |
| 6 | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |

Combining MADRS item scores 0 and 1, 35.3% - 39.2% had little or no suicidal ideation prior to treatment.

4.3 HAMD Suicide Item - Change over time

Scores on the HAMD suicide item across treatment groups over time are displayed in Table 7. Differences are expressed as change from baseline. The active controls are the same as described in Section 4.1.

*Table 7*
HAMD Suicide Item: Difference from Baseline

| | Baseline | Week No. 1 | 2 | 4 | 6 |
|---|---|---|---|---|---|
| Paroxetine | 1.3 n=2852 | -0.5* n=2552 | -0.8* n=2504 | -1.0* n=2200 | -1.1* n=1959 |
| Placebo | 1.3 n=554 | -0.3 n=530 | -0.5 n=495 | -0.6 n=398 | -0.8 n=275 |
| Active control | 1.3 n=1101 | -0.5* n=1029 | -0.7* n=963 | -0.9* n=829 | -1.0* n=710 |

*Par vs Pla P<0.05
*Act vs Pla P<0.05

The scores of paroxetine-treated subjects and the other active controls showed improvement compared to placebo at all post-baseline assessments, in the ability to reduce the level of suicidal thinking in patients with pre-existing suicidal thoughts.

4.4 MADRS Suicide Item - Change over time

Scores on the MADRS suicide item across treatment groups over time are displayed in Table 8. Differences are expressed as change from baseline. The active controls are the same as described in Section 4.2.

*Table 8*
MADRS[1] Suicide Item: Difference from Baseline

| | Baseline[2] | Week 1 | Week 2 | Week 3 | Week 4 | Week 6 |
|---|---|---|---|---|---|---|
| Paroxetine | 1.83 n=1510 | -0.53 n=1457 | -0.83 n=1320 | -1.00 n=1218 | -1.17 n=1162 | -1.28 n=1050 |
| Placebo | 1.82 n=459 | -0.28 n=446 | -0.55 n=425 | -0.66 n=377 | -0.84 n=362 | -0.92 n=248 |
| Act.Controls | 1.78 n=454 | -0.41 n=444 | -0.73 n=392 | -0.78 n=355 | -0.96 n=313 | -1.14 n=264 |
| Pairwise Comparisons[3] | | | | | | |
| Parox. vs Placebo | | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 |
| Parox. vs Other Active | | 0.0075 | 0.1258 | 0.0011 | 0.0071 | 0.0713 |
| Placebo vs Other Active | | 0.0375 | 0.0129 | 0.0832 | 0.0895 | 0.0663 |

[1] Only studies performed in the U.S. used the MADRS scale.
[2] ANOVA p = 0.56 for baseline treatment comparison.
[3] P-values based on the Wilcoxon rank-sum test.

The scores of paroxetine-treated subjects showed improvement compared to placebo controls at all post-baseline assessments in the ability to reduce the level of suicidal thinking in patients with pre-existing suicidal thoughts. The scores of subjects on other active control regimens were improved compared to placebo only at weeks 1 and 2.

4.5 Emergence of Suicidality

The relation between pharmacotherapy and the emergence of suicidality was assessed. "Emergent suicidal thoughts" were defined for those patients who had a baseline score of 0 or 1 on the HAMD suicide item and developed a score of 3 or 4 at any time during the six week course of therapy. Results are presented in Table 9.

*Table 9*
Emergence of Suicidal Thoughts
at any time during 6 weeks of therapy
HAMD Suicide Item Score = 0 or 1 at Baseline

| Paroxetine n=1659 | Placebo n=331 | Active Controls n=683 |
|---|---|---|
| n (%) | n (%) | n (%) |
| 29 (1.7) | 5 (1.5) | 9 (1.3) |
| Par vs Pla P>0.90 | Act vs Pla P=0.78 | |
| Par vs Act P=0.59 | | |

No significant differences were seen among the paroxetine, placebo and active control groups.

The HAMD suicide item is not an interval scale. Thus, differences between any two ratings are unlikely to be clinically equivalent. A change from 0 to 1 is clinically very different from a change of 1 to 2. Because of this non-linearity, a further analysis considered the emergence of suicidality over 6 weeks of therapy in patients who had no suicidal thoughts (score = 0) at baseline. Results are given in Table 10.

*Table 10*
Emergence of Suicidal Thoughts
at any time during 6 weeks of therapy
HAMD Suicide Item Score = 0 at Baseline

| Paroxetine n=708 | Placebo n=126 | Active Controls n=317 |
|---|---|---|
| n (%) | n (%) | n (%) |
| 136 (19) | 44 (35) | 63 (20) |
| Par vs Pla P<0.001 | Act vs Pla P<0.001 | |
| Par vs Act P=0.80 | | |

No difference was seen between paroxetine and active control. In this analysis however, paroxetine and other antidepressant drugs produced significantly less emergent behavior than did placebo ($p<0.001$).

A distribution of emergent scores over 6 weeks of therapy in patients who had a score 0 at baseline is displayed in Table 11.

*Table 11*
Distribution of emergence of suicidal thoughts in patients with HAMD Suicide Item Score = 0 at baseline

| | HAMD emergent score | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| | % | % | % | % |
| Paroxetine (n=708) | 16 | 3 | 0.6 | 0 |
| Placebo (n=126) | 26 | 7 | 2 | 0 |
| Active Control (n=317) | 15 | 3 | 2 | 0 |

As can be seen, the distribution of emergent suicidality of differing severity (scores 1, 2, 3 or 4 on the HAMD suicide item), was similar between paroxetine and active control. As in the previous analysis, the emergence of suicidal thoughts was greater in the placebo-treated patient group.

Moreover, placebo-treated patients with no suicidality at baseline still displayed emergent suicidal thoughts. This suggests that the emergence of suicidal thoughts is intrinsic to depressive illness.

4.6 HAMD Suicide Item - Retardation Item Dissociation.

Improvement in retardation prior to alleviation of suicidal ideation can lead to intensification of suicidal thoughts and behavior. An analysis was conducted to assess the dissociation of psychomotor retardation and suicidality. Psychomotor retardation was assessed using Item #8 of the HAMD scale and is rated as follows:

0 = normal speech and thought
1 = slight retardation at interview
2 = obvious retardation at interview
3 = interview difficult
4 = complete stupor

Patients who at any time during therapy, had a HAMD suicide item score of at least 2 points greater than the HAMD retardation item score were considered to be "at risk".

Results are presented in Table 12.

*Table 12*
Suicide item score - Retardation item score by treatment

| "At Risk" | Paroxetine n | Paroxetine % | Placebo n | Placebo % | Active Control n | Active Control % |
|---|---|---|---|---|---|---|
| No | 2668 | 95.7 | 506 | 93.9 | 1038 | 96.2 |
| Yes | 120 | 4.3 | 33 | 6.1 | 41 | 3.8 |
| No post-baseline data | 64 | | 15 | | 22 | |
| Total | 2852 | | 554 | | 1101 | |

Par vs Pla P = 0.07
Par vs Act P = 0.53
Act vs Pla P = 0.04

The percentage of patients with a dissociation between psychomotor retardation scores and suicide item scores tended to be higher among the placebo group (6.1%), than for those in the paroxetine (4.3%) or active control (3.8%) groups.

## 4.7 Anger/Hostility subcluster - Change-over Time

Anger and hostility, assessed by The Anger/Hostility subcluster items of the patient-rated Hopkins Symptom Checklist (SCL-56), can be expressed both inwardly and outwardly. Inwardly directed anger and hostility may manifest itself as violence toward oneself. Thus, the effect of paroxetine on this parameter was analyzed. Results are displayed in Table 13.

*Table 13*
Anger/Hostility Subcluster of SCL-56: Difference from Baseline

| | Baseline[1] | Week 1 | Week 2 | Week 3 | Week 4 | Week 6 |
|---|---|---|---|---|---|---|
| Paroxetine | 4.27<br>n=868 | -0.60<br>n=868 | -0.85<br>n=771 | -0.99<br>n=722 | -1.10<br>n=669 | -1.25<br>n=561 |
| Placebo | 4.22<br>n=430 | -0.10<br>n=430 | -0.15<br>n=414 | -0.20<br>n=367 | -0.45<br>n=314 | -0.67<br>n=239 |
| Act.Controls | 4.25<br>n=355 | -0.42<br>n=355 | -0.61<br>n=317 | -0.69<br>n=285 | -0.76<br>n=244 | -0.88<br>n=212 |
| Pairwise Comparisons[2] | | | | | | |
| Parox. vs Placebo | | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Parox. vs Other Active | | 0.0606 | 0.0212 | 0.0075 | 0.0061 | 0.0067 |
| Placebo vs Other Active | | 0.0019 | <0.0001 | <0.0001 | 0.0228 | 0.1823 |

[1] Anova p = 0.85 for baseline treatment comparison
[2] P values based on Anova

Treatment with paroxetine resulted in significant improvement in Anger/Hostility scores at all post-baseline assessments, compared to placebo. The scores of subjects on other active control regimens were significantly improved compared to placebo at Weeks 1-4 but not at Week 6. Moreover, the scores of subjects on paroxetine were significantly improved compared to those of subjects on active treatment regimens at Weeks 2 through 6.

Discussion and Conclusions

A review of the worldwide clinical database was conducted using data which were submitted in support of the product license application for paroxetine. This review of data from clinical studies of depression revealed that:

1) The incidence of suicides in patients randomized to paroxetine did not differ substantively from the incidence of suicides in patients randomized to placebo or to other active control regimens.

2) The incidence of attempted suicides did not differ substantively among the three treatment groups (paroxetine, placebo, active controls).

3) The incidence of attempted suicides by overdose did not differ substantively among the three treatment groups (paroxetine, placebo, active controls).

4) Suicidality, reported as an adverse event in the worldwide database, was reported with similar incidence in each of the treatment groups.

5) Based on the change in scores of the HAMD and MADRS suicide items, both paroxetine and other active treatments have been shown to significantly reduce the level of suicidal thinking in patients with pre-existing suicidal ideation. Moreover, results of the MADRS suicide item indicate that scores were significantly more improved by paroxetine than by the other active control regimens considered in this report.

6) Based on the change from baseline of the Suicide Item of the Hamilton Depression Scale (HAMD-3), no significant differences were observed among treatment groups in the emergence of suicidal thoughts of patients who entered the study with no or only mild suicidal thoughts (i.e., Baseline score = 0 or 1). However, when one considers a patient cohort having no suicidal thoughts or tendencies at the inception of the study (i.e., Baseline score = 0), then patients randomized to paroxetine and other active control regimens had significantly fewer emergent suicidal thoughts than patients randomized to the placebo regimen. Furthermore, the distribution of scores for emergent suicidal thoughts indicates that the degree of severity was less for paroxetine and the active controls, when compared to placebo. The appearance of suicidal ideation in placebo-treated patients previously devoid of suicidal thoughts is consistent with the phenomenon being intrinsic to depressive illness.

7) Paroxetine and other active treatments produce significant improvement in the scores of the Anger/Hostility subcluster of the Hopkins' Symptom Checklist. Moreover, scores were significantly more improved by paroxetine than by other active treatments after only 1 week on therapy.

In summary, suicidal ideation and behavior is an inherent risk when treating patients with major depressive disorder[20]. Moreover, it is now recognized that intensification of suicidal thoughts and behavior can occur in depressed patients undergoing active treatment, including antidepressant pharmacotherapy.[16-19] Nevertheless, analyses of our prospective, clinical trials for depression show that patients who were randomized to paroxetine therapy were at no greater risk for suicidal ideation or behavior than were patients randomized to placebo or other active control therapies.

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APPENDIX 1

Suicides

| PAROXETINE | | PLACEBO | | ACTIVE CONTROLS | |
|---|---|---|---|---|---|
| PID | Duration of Therapy (Days) | PID | Duration of Therapy (Days) | PID | Duration of Therapy (Days) |
| 1 13 126 | 144 | 7119 009* | -7 | 237I 054 | 74 |
| 2206 005 | 182 | 7119 062* | -2 | 6 67 002 | >49 |
| 2406 149 | 45 | | | 7124 023 | 18 |
| 647 003 | 47 | | | | |
| 7124 012 | 10 | | | | |

*Suicides were committed during the placebo wash-out phase of an active control study. These acts were committed 2 days and 7 days prior to the baseline evaluation (i.e., -2 and -7 days).

APPENDIX 2

Attempted Suicides by Overdose
by Patients Randomized to Paroxetine

| PAROXETINE | | PAROXETINE plus OTHER ACTIVE AGENTS | | OTHER ACTIVE AGENTS | |
|---|---|---|---|---|---|
| PID | Duration of Therapy (Days) | PID | Duration of Therapy (Days) | PID | Duration of Therapy (Days) |
| 1 41 336 | 330 | 1 13 149 | 21 | 1 13 010 | 180 |
| 2323 051 | 28 | 1 32 018 | 15 | 1 14 045 | 270 |
| 02 04 089 | 42 | 1 41 323 | 90 | 1 26 001 | 10 |
| 04 01 009 | 224 | 7101 019 | 30 | 1 41 303 | 21 |
| 05 01A 030 | 35 | 1 41 384 | 35 | 1 41 330 | 120 |
| 09 01A 005 | * | 05 02F 002 | 7 | 1 41 372 | 28 |
| 1 13 155 | 10 | | | 2229 014 | 330 |
| 1 41 340 | 2 | | | 7124 015 | 42 |
| 6162 005 | 4 | | | 647 003 | 42 |
| | | | | 04 06 096 | 112 |
| | | | | 05 01A 075 | >1092 |
| | | | | 05 02B 019 | 56 |
| | | | | 09 01E 260 | * |

* data missing

SUIC.
4/29/91

APPENDIX 3

Attempted Suicides other than by overdose for patients randomized to paroxetine

Lacerations

| PID | Days on Therapy |
|---|---|
| 1 13 144 | 14 |
| 1 17A 004 | 3 |
| 2206 021 | 72 |
| 2502 004 | 1 |
| 04 02 056 | 21 |

Hanging

| PID | Days on Therapy |
|---|---|
| 237G 109 | 3 |

Defenestration

| PID | Days on Therapy |
|---|---|
| 2112 004 | 28 |
| 7101 007 | 84 |
| 07 01A 001 | 21 |
| 09 01J 573 | 21 |

Unknown

| PID | Days on Therapy |
|---|---|
| 7119 012 | 5 |

CO Poisoning

| PID | Days on Therapy |
|---|---|
| 1 14 029 | 70 |

PAR000898186