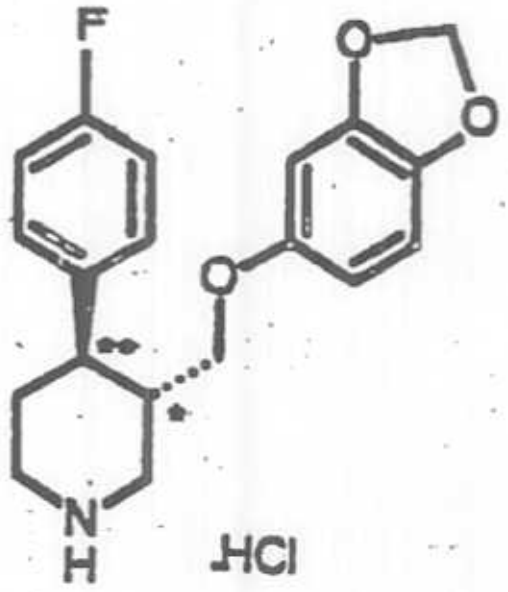
REVIEW AND EVALUATION OF CLINICAL DATA

ORIGINAL NDA 20-031

PAROXETINE (AROPAX®)

SAFETY REVIEW



Reviewer: Martin Brecher M.D., D.M.Sc.

Sponsor: SmithKline Beecham Pharmaceuticals

Date: June 19, 1991

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bed. The frequency of pulmonary embolism in the medically ill population, the infrequency of embolism in the paroxetine population, the absence of other embolic events and the absence of other manifestations of coagulopathy render it difficult to attribute these 2 fatal pulmonary emboli to paroxetine.

Deaths-Suicide.
An additional 15 patients, all enrolled in European trials, (7 paroxetine, 1 imipramine, 1 fluvoxamine, 1 amitriptyline and 5 placebo) committed suicide. The method was provided in 10 of the cases, but none of the deaths was attributable to overdosage of paroxetine. The minimum lethal dose is therefore unknown. Two of the five placebo suicides occurred during run-in.

A 58 year old woman receiving paroxetine (Belgian open study 2206.005 patient Vol. 1.408 p.281) committed suicide by hanging in the fifth month of treatment. No further information is available.

A 42 year old woman (Study DFC124 patient Vol. 1.416 p. 217) on an unstated dose of paroxetine took a fatal overdose of doxepin.

A patient on placebo (Vol. 1.416, p.120) committed suicide.

A 50 year old man (Study MDUK13 patient Vol. 1.411 p. 290) on 30 mg/d paroxetine committed suicide by hanging on the 144th day of treatment. All adverse events had resolved by the time of the suicide.

An 18 year old woman (Study 29060 patient Vol. 1.414 p. 199) discontinued paroxetine on day 38 and committed suicide by overdosage on day 44. She received Valium from day 32. Details regarding the pills consumed were not provided.

A 56 year old woman (Study HP/82/47 patient Vol. 1.414 p. 344) on 30 mg paroxetine killed herself by drowning on day 47.

A 51 year old man (Protocol 058/022) on an unknown dose of paroxetine committed suicide in June 1990.

A 66 year old man (Study 29060 patient Vol. 1.415 p. 230) received clomipramine for 6 weeks before being switched to fluvoxamine. One month later he committed suicide by hanging.

A 36 year old man (Study HP/83/67 patient Vol. 1.415 p. 276) who improved on 150 mg/d amitriptyline committed suicide by undescribed means.

A 58 year old man (DFC124 patient Vol 1.416 p. 226) receiving imipramine killed himself with a firearm.

A 49 year old man (7119.009 Vol. 1.408 p.295) committed suicide during the placebo run-in phase.

A 43 year old man (Study DFC119 patient Vol. 1.416 p. 152) committed suicide during the placebo run-in of the study.

Patient (Annual report) received placebo and committed suicide by drowning.

An 80 year old man (Annual report, patient# on placebo committed suicide by hanging.

A 58 year old woman (Study 29060/083 patient Update Vol 24.3 p. 1) committed suicide by hanging on day 8 of paroxetine treatment.

Deaths-Other Causes

A 55 year old woman (patient Vol. 1.408, p. 287) being treated with paroxetine was murdered.

Suicide Attempts

59 additional patients attempted suicide. 14 of these patients were enrolled in U.S. trials; the remainder were enrolled in Europe. The 14 U.S. patients included 12 on paroxetine, 1 on imipramine and 1 on placebo. The 45 foreign suicide attempts included 30 paroxetine patients, 13 patients who received an active control and 2 placebo patients. The largest overdose of paroxetine was 850 mg. This patient was admitted to the hospital in a semi-obtunded state and thereafter showed steady improvement. The next largest overdose was 420 mg which resulted in admission to the hospital with symptoms of mydriasis, dry mouth and sinus tachycardia. The patient was discharged the following day. Another patient took a 360-400 mg overdose of paroxetine. This patient was obtunded when admitted to the Emergency Room, but was alert 7 hours later.

42 of the 59 suicide attempts (71.8%) were made by patients on paroxetine who comprised 63.5% of the patients in the Phase II-III trials. However the paroxetine patients were exposed and observed for longer durations rendering the distribution of suicide attempts unremarkable.

Overview of Suicidality

Given current concern that a small proportion of depressed patients may develop unprecedented, obsessive and severe suicidal ideation on serotonin reuptake inhibitors we asked the sponsor to analyze the data base for emerging suicidality. The sponsor submitted an analysis of the NDA data base of 4,668 patients of whom 2963 received paroxetine, 1151 received an active control and 554 received placebo. Suicidality was counted as an adverse event if the following adverse events were noted in the clinical record: suicidal ideation, suicide risk, ideas of suicide, suicidal thoughts, suicidal tendency, parasuicidal tendency, felt suicidal, became suicidal, suicidal feelings and suicidal threats. Table 13 lists the results for the three treatment groups.

TABLE 13
Suicidality in Paroxetine Clinical Trials

	Paroxetine N=2963 1008 P.E.Y.*	Placebo N=554 72 P.E.Y.	Active Control N=1151 218 P.E.Y.
Completed Suicides			
No. (%)	5 (0.17)	2 (0.36)	3 (0.26)
No./P.E.Y.	0.005	0.028	0.014
Attempted Suicides			
No. (%)	40 (1.3)	6 (1.1)	12 (1.0)
No./(P.E.Y.)	0.040	0.083	0.055
Suicidality Reported as an Adverse Event			
No. (%)	13 (0.4)	2 (0.4)	5 (0.4)
No./P.E.Y.	0.013	0.028	0.023

* P.E.Y. stands for Patient Exposure Years

The values for paroxetine did not exceed those of the other two groups for any of the 6 measures.

The sponsor also estimated the frequency of emergent suicidal ideation by counting the number of patients with a baseline score of 0 or 1 on the Hamilton Depression Scale suicide item (item #3) who developed significant suicidal ideation at any point during a six week trial as measured by a score of 3 or 4 on the suicide item. The results of this analysis were:

Paroxetine N=1659 N (%)	Placebo N=331 N (%)	Active Control N=683 N (%)
29 (1.7)	5 (1.5)	9 (1.3)

Parox. vs. Placebo p >0.9; Parox. vs. Active p =0.59; Active vs. Placebo p =0.78

Although the instruments available may not be ideal to capture the elusive clinical events reported by Teicher in 6 patients, there is no signal in this large data base that paroxetine exposes a subset of depressed patients to additional risk for suicide, suicide attempts or suicidal ideation.

Myocardial Ischemia and Congestive Failure

Patient (Vol. 1.410 p. 56), a 47 year old man, was discontinued from 50mg/d on the 103rd day of treatment after an ECG revealed T wave changes (isoelectric T-wave in leads V4-6) compatible with myocardial ischemia. The patient did not have cardiac symptoms and lab values and a chest X-ray remained normal. No ischemic changes were noted on stress testing two weeks after discontinuation. The consulting cardiologist considered the patient's abnormal repolarization to be a normal variant.

Patient who received 40 mg/d paroxetine for 39 months had an angiographically confirmed anterior wall myocardial infarction. He had a history of smoking and hypercholesterolemia. This case was not reported in the list of dropouts and was discovered in the sponsor's correspondence file (Vol. 12 of 14, p. 3003).

The sponsor's proposed listing of other events, particularly for the nervous and gastrointestinal systems which are the major loci of paroxetine's adverse events, contain numerous other errors of commission and omission. These lists contain items which have already been listed in the previous table and omit other adverse events which should be listed. The sponsor will need to revise these lists.

SUMMARY

Review of the well organized safety database did not reveal any serious toxicity attributable to paroxetine. The side effect profile of paroxetine is similar to that of selective serotonin reuptake inhibitors and different from that of the tricyclic antidepressants. The accompanying efficacy review found paroxetine to be an effective antidepressant. Together the safety and efficacy data allow the conclusion that paroxetine is safe and efficacious and approvable for marketing.

Martin Brecher

Martin Brecher, M.D., D.M.Sc.
June 19, 1991

cc: Original NDA, 20-031
HFD-120
HFD-120/P Leber
/T Laughren
/M Brecher
/P David

10-5-92

I have reviewed Dr. Brecher's findings and, in addition, I have reviewed the 2-13-92 safety update that increased the population of paroxetine exposures in premarketing studies to approximately 5100 patients. The safety and efficacy findings for paroxetine were presented to the PDAC on this date (10-5-92), and they unanimously agreed that paroxetine has been demonstrated to be safe and effective. I agree that these data do not reveal any safety findings that would preclude the approvability of paroxetine for use in depression. My written review of the safety update, will follow shortly, and I will provide more detailed comments on safety issues in my supervisory memo, also to follow. I have prepared the clinical sections of the draft SBA and the draft labeling that will accompany the approvable package.

Thomas P. Laughren, MD
Group Leader, PDP