PROJECT: IND 23280 - PAROXETINE (BRL 29060)

INTEGRATED SUMMARY OF SAFETY INFORMATION
PAROXETINE CLINICAL TRIALS PROGRAM

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	Paroxetine (n=2963)	Placebo (n=554)
Mean Age (yrs)	46.70	42.02
Minimum Age (yrs)	17	19
Maximum Age (yrs)	94	73
Mean Weight (lbs)	156.92	165.61
Age Groups		
<40 years	1112 (38%)	269 (49%)
40-64 years	1386 (47%)	263 (48%)
≥65 years	459 (16%)	22 (4%)
Unknown	6 -	
Sex		
Female	1864 (63%)	286 (52%)
Male	1098 (37%)	268 (48%)
Unknown	1 -	
Race		
White	2571 (94%)	513 (93%)
Black	81 (3%)	29 (5%)
Other	94 (3%)	12 (2%)
Unknown	217 -	

Note: In this table, all patients who crossed over

Table I.3

Demographic Information

Total Worldwide Patient Enrollment

Presented by Treatment Group

Imipramine (n=338)	Amitriptyline (n=331)	Clomipramine (n=193)	Mianserin (n=150)	Doxepin (n=135)	Maprotiline (n=4)
40.46	43.64	57.27	49.98	68.19	56.75
18	17	21	17	60	46
74	82	96	87	82	63
157.26	145.17	141.49	147.79	159.62	-
169 (50%)	147 (44%)	29 (15%)	45 (30%)	-	-
159 (47%)	161 (49%)	99 (52%)	76 (51%)	33 (24%)	4 (100%)
10 (3%)	23 (7%)	63 (33%)	29 (19%)	102 (76%)	-
		2 -			
174 (51%)	240 (73%)	136 (70%)	99 (66%)	73 (54%)	3 (75%)
164 (49%)	91 (27%)	57 (30%)	51 (34%)	62 (46%)	1 (25%)
304 (93%)	238 (95%)	89 (67%)	144 (97%)	131 (97%)	4 (100%)
17 (5%)	8 (3%)	-	2 (1%)	4 (3%)	-
6 (2%)	4 (2%)	43 (33%)	3 (2%)	-	-
11 -	81 -	61 -	1 -	-	-

from one treatment to another are counted twice, once for each of their treatment groups.

Table I.5 (Cont.)

Comparison of Adverse Experiences Listed By

Preferred Term Within Body System

Intent-to-Treat Population - Worldwide Data

Events Reported in At Least 1% of Paroxetine Patients

Body System	Preferred Term	Paroxetine (N=2963)	Placebo (N=554)
Nervous System			
	Abnormal Dreams	59 (2%)	4 (1%)
	Agitation	115 (4%)	11 (2%)
	Amnesia	34 (1%)	4 (1%)
	Anxiety	146 (5%)	14 (3%)
	CNS Stimulation	110 (4%)	18 (3%)
	Concentration Impaired	77 (3%)	2 (0%)
	Confusion	43 (1%)	4 (1%)
	Depersonalization	27 (1%)	1 (0%)
	Depression	34 (1%)	2 (0%)
	Dizziness	328(11%)	32 (6%)
	Drugged Feeling	37 (1%)	4 (1%)
	Emotional Lability	42 (1%)	2 (0%)
	Insomnia	410(14%)	40 (7%)
	Lack of Emotion	19 (1%)	1 (0%)
	Libido Decreased	94 (3%)	0 (0%)
	Manic Reaction	27 (1%)	2 (0%)
	Myoclonus	45 (2%)	3 (1%)
	Nervousness	109 (4%)	12 (2%)
	Paresthesia	150 (5%)	12 (2%)
	Somnolence	606(20%)	49 (9%)
	Tremor	320(11%)	10 (2%)
	Vertigo	46 (2%)	1 (0%)

Table I.7

Comparisons for Adverse Experiences

Number of Patients Whose Dosage was Permanently Stopped

Due to Adverse Experiences

World-Wide Intent-to-Treat Population

Adverse Experience Preferred Term	Paroxetine (n=523)	Placebo (n=29)	All Other (n=258)
Nausea	121* (23%)	6 (21%)	36 (14%)
Somnolence	84 (16%)	4 (14%)	67 (26%)
Insomnia	66 (13%)	3 (10%)	19 (7%)
Headache	65 (12%)	7 (24%)	28 (11%)
Asthenia	60 (11%)	3 (10%)	39 (15%)
Dizziness	47 (9%)	4 (14%)	44 (17%)
Tremor	44 (8%)	2 (7%)	25 (10%)
Diarrhea	36 (7%)	2 (7%)	6 (2%)
Agitation	33 (6%)	4 (14%)	10 (4%)
Sweating	33 (6%)	2 (7%)	23 (9%)
Dry Mouth	32 (6%)	2 (7%)	74 (29%)
Vomiting	30 (6%)	0 (0%)	5 (2%)
Anxiety	29 (6%)	1 (3%)	16 (6%)
Abdominal Pain	26 (5%)	1 (3%)	7 (3%)
Decreased Appetite	24 (5%)	3 (10%)	10 (4%)
Constipation	24 (5%)	3 (10%)	24 (9%)
Weight Gain	19 (4%)	0 (0%)	4 (2%)
Hypertension	18 (3%)	0 (0%)	3 (1%)
Palpitation	17 (3%)	3 (10%)	19 (7%)
Paresthesia	17 (3%)	0 (0%)	18 (7%)
CNS Stimulation	17 (3%)	4 (14%)	15 (6%)
Blurred Vision	17 (3%)	0 (0%)	12 (5%)
Emotional Lability	16 (3%)	0 (0%)	11 (4%)
Abnormal Ejaculation*	15 (9%)	0 (0%)	2 (2%)
Confusion	14 (3%)	0 (0%)	13 (5%)
Chest Pain	13 (2%)	0 (0%)	2 (1%)
Manic Reaction	12 (2%)	1 (3%)	11 (4%)
Malaise	11 (2%)	0 (0%)	8 (3%)
Urination Impaired	11 (2%)	0 (0%)	14 (5%)
Tachycardia	10 (2%)	1 (3%)	7 (3%)
Vertigo	6 (1%)	0 (0%)	10 (4%)

* All percentages are with respect to the number of patients in the drug group who discontinued treatment due to adverse experience. Denominator reflects gender.

3. SERIOUS ADVERSE EXPERIENCES

a. Deaths

Thirteen deaths occurred during or soon after paroxetine treatment in the world-wide clinical program. No deaths were considered to be associated with paroxetine administration.

b. Overdoses

Overdoses are to be expected in a depressed population. Twenty overdoses were reported in paroxetine-treated patients. All cases in which paroxetine was overdosed responded with a full recovery.

4. SEVERE ADVERSE EXPERIENCES

Table I.8 illustrates the comparison of treatment groups showing the severity of the adverse experience. In this comparison, paroxetine is associated with an intermediate rate of reporting at least one adverse experience, at least one moderate or severe adverse experience, and at least one severe adverse experience when compared to placebo and other antidepressants.

The safety summary includes searches of the world-wide data for groups of symptoms associated with antidepressants such as the zimelidine reaction, serotonin syndrome, bleeding diathesis, and sexual dysfunction. Also, rare adverse experiences which can be organ- or life-threatening are discussed in detail. Recognizing the limitations in retrospective review of a database, few reports of serious illness have been associated with paroxetine treatment. In at least 3 individual cases, the possibility of a relationship between paroxetine and single reports of erythema nodosum, pulmonary alveolitis, and transient liver enzyme elevation cannot be excluded.

8. CONCLUSIONS

The integrated summary of safety information provides support for the use of paroxetine in treatment of depression. Paroxetine is a specific serotonin reuptake inhibitor with biologic actions which are responsible for therapeutic response and actions which can be adverse. Paroxetine has demonstrated a favorable risk/benefit ratio which can be of significant benefit in the treatment of depression.

PAR 03-03-113 (Paroxetine-treated)
PAR 04-03-113 (Paroxetine-treated)

The patient is a 32-year-old white female who entered the study on 7/03/86 with a diagnosis of major depression, recurrent, (DSM-III 296.30). She was in good general health and no known drug allergies were reported.

Screening laboratory studies, ECG, chest x-ray, and ophthalmologic exam revealed no significant abnormalities.

On 7/10/86 the patient began paroxetine 20 mg/day and progressed to 50 mg/day. She was on drug 42 days under this protocol. No adverse clinical experiences were reported during this portion of the study. She elected to continue on paroxetine 50 mg/day in the 1-year extension study.

On 10/30/86 the patient was seen in the emergency room with acute alcohol intoxication. There originally was some question of a possible suicide attempt but it was later felt that this was merely an attempt to "drown her sorrows." There was no evidence that drugs other than alcohol were involved at this admission. She continued on paroxetine until 11/03/86 when she was discharged from the hospital and terminated from the study due to alcohol abuse. She was on drug for 75 days.

On 11/04/86 she was admitted to the Philadelphia Psychiatric Center (PPC) for further evaluation and treatment of her depression and recent ETOH intoxication. She was discharged on 11/11/86 (against medical advise). She was voluntarily re-admitted to PPC 11/21/86 and was treated with lithium, milieu therapy, activities therapy, and group therapy. Urine specimen was noted to be positive for cannabinoids. She also required treatment of a viral bronchitis while hospitalized. The patient was discharged on 12/10/86 in improved condition. She was continued on lithium and psychotherapy.

After having shown an initial good response to paroxetine (HAMD score at screen was 26 and at day 70 was 3) she had a marked deterioration in her depressive symptoms with acute ETOH intoxication and subsequent hospitalization.

10. DEATHS

A total of 17 deaths were reported in the paroxetine worldwide clinical program. An overview of the 17 deaths is presented in Table X.17 below.

Table XI.17
Deaths Reported in Worldwide Clinical Trial Program

	PAROXETINE N=2963	ACTIVE CONTROL N=531	PLACEBO*
Number (%)	12 (0.4%)	3 (0.56%)	2

* Two deaths occurred during the placebo run-in period.

One death occurred in the U.S. clinical trial program (Pt. No. 04-01-022). The narrative summary of this death follows this summary. The death occurred in a patient with a history of hypertension, obesity, diabetes mellitus, and alcohol abuse. Death occurred approximately 26 days after the last paroxetine administration.

Eleven deaths were reported in patients randomized to paroxetine treatment in non-U.S. clinical trials. An overview of the worldwide data on deaths in paroxetine-treated patients is shown in Table XI.18.

Table XI.18

Causes of Deaths in Patients Randomized to Paroxetine - Worldwide Data

Pre-existing conditions PIDs: 1.26.034; 117A.004; 1.14.34; 2113.003; 7101.015	4
Sudden death - MI (U.S. patient) PID: 4.01.022	1
Sudden death - MI (U.K. patient) PID: 1.13.028	1
Murder PID: 4.02.010	1
Suicide PIDs: 1.13.126; 2206.005; 6.47.003	3
Overdose PIDs: 2406.149; 7124.012	2
TOTAL	12

Since suicide is a not unexpected complication of clinically significant depression, a small number of successful suicides are to be expected in a depressed population. In one case of suicide (HP/82/47 Patient 3), the patient committed suicide by drowning. The investigator reported that her clinical state, as measured by the Hamilton Depression Rating Scale, had improved during the course of the trial, potentially giving her the volition to kill herself. The relationship between paroxetine treatment and this suicide is speculative. Paroxetine has not been associated as a causative factor with any deaths during the worldwide clinical trial program.

There were five other deaths by suicide. Two were during the placebo washout phase (PIDs: 7119.009 and 7119.062). Three were in comparative treatment groups: Amitriptyline (PID 6.67.002), clomipramine (PID 237I.054), and imipramine (PID 7124.023).

PAR 03-01-022 (Imipramine-treated)
PAR 04-01-022 (Paroxetine-treated)

The patient was a 54-year-old male who entered the study on 07/23/85 with a diagnosis of major depressive disorder, recurrent, with melancholia (DSM-III 296.33). He had a past medical history of appendectomy (1944) and tonsillectomy (1955) and occasional headaches. He was also obese and hypertensive. There were no reported drug allergies. Concomitant medications at that time were aspirin prn headache, ADVIL® (ibuprofen) unit dose prn flu symptoms (8/12/85-8/25/85), and KAOPECTATE® (kaolin and pectin) prn diarrhea (8/12/85-8/25/85). Screening laboratory results revealed no significant abnormalities. Screening ECG revealed LAD and an intraventricular conduction defect reported not clinically significant by the investigator. Dr. Charles Fisch, Distinguished Professor of Medicine at Indiana University, who reviewed all ECGs for this study also noted a RBBB. Chest x-ray was normal. His pulse rate varied from a low of 80 beats per minute to a high of 100 beats per minute during the study. Dr. Fisch noted that the "acceleration of heart rate with imipramine is a recognized effect of the drug.". (Imipramine was the drug taken by this patient in the 03 study.)

Adverse experiences reported during the study were severe profuse sweating (probably drug-related) 8/11/85-9/03/85; severe diarrhea (possibly drug-related) 8/11/85-8/25/85; and severe stomach upset (possibly drug-related) 8/11/85-8/25/85. Patient was noted to have elevated blood sugar and liver function tests on 2 occasions felt to be due to lipemic serum. It should also be noted that he had elevated cholesterol and triglyceride levels through his participation in the Protocol 03 study. ST segment changes in V1 and V2 occurred at visit 21, and at visit 42 ST segment changes were noted in V1 only. These ECG changes were reported not clinically significant by the investigator. According to Dr. Fisch the effects of imipramine, on "the ST and T changes (in the ECGs) were minor, largely transient, non-specific and probably of no clinical significance."

On 7/24/85 the patient began imipramine 80 mg/day (days 1-7). His dose was then increased to 145 mg/day (days 8-14) and to 210 mg/day (days 15-42). He took imipramine for 42 days. Due to lack of efficacy, the patient was crossed over to paroxetine in this 1-year, double-blind extension of study 03.

On 9/04/85 the patient began paroxetine 20 mg/day (days 1-14) and increased to 30 mg/day (days 15-278). On 6/23/86 the patient was prematurely terminated from the study due to a non-drug-related reason: "TIA and newly diagnosed diabetes mellitus." However, upon review of the case report form by the clinical monitor, the termination reason was recoded to adverse experience. This is due to the fact that the patient's TIA and newly diagnosed diabetes mellitus were listed as adverse experiences and were identified as the reason for premature termination.

PAR 04-01-022 (Cont.)

Concomitant medications used during the 1-year extension of the study were aspirin prn headache (taken since 1965); NYQUIL® (acetaminophen, doxylamine succinate, pseudoephedrine HCl and dextromethorphan hydrobromide) unit dose prn cough (1/29/86 to 1/30/86); cough syrup, (OTC, brand unknown) 2-3 tsp/day prn cough (1/29/86 to 2/04/86); MICRONASE® (glyburide) 5 mg/daily for diabetes (6/17/86 - continues); and DYAZIDE® (hydrochlorothiazide and triamterene) one daily for hypertension (6/18/86 - continues).

Adverse clinical experiences reported during the extension phase of the study were severe sweating (possibly drug-related) which resolved after discontinuation of drug; mild nightmares 9/04/85-10/08/85 (possibly drug-related); mild palpitations 9/11/85-9/19/85 (possibly drug-related); mild urinary retention 9/05/85-9/18/85 (probably drug-related); mild muscular soreness 9/05/85-10/16/85 (possibly drug-related); severe headaches 9/05/85-11/13/85 (probably drug-related); mild itching 9/13/85-9/26/85 (possibly drug-related); mild hay fever symptoms 9/13/85-12/16/85 (probably not drug-related); mild tightness in right leg muscle 9/22/85-11/13/85 (possibly drug-related); moderate agitation by noise 9/20/85-11/13/85 (possibly drug-related); moderate lethargy 9/18/85 - resolved after discontinuing medication (probably not drug-related); mild chest pains 12/11/85-12/15/85 (probably not drug-related); mild cough 1/29/86-2/14/86 (definitely not drug-related); moderate transient ischemic attack 6/15/86-6/21/86 (probably not drug-related); and mild diabetes mellitus 6/15/86 - continues (probably not drug-related). Concomitant medications and underlying disease states may have caused many of these adverse clinical experiences.

Adverse laboratory experiences reported were mildly elevated blood sugar on 9/10/85, 9/24/85, and 10/16/85 (non-fasting specimens), mild elevations of SGOT (ranging from a normal value of 33 U/L to a high of 91 U/L), SGPT (ranging from a low of 84 U/L to a high of 150 U/L), cholesterol, and triglycerides. These values (SGPT, cholesterol, and triglycerides) were elevated on all tests whether fasting or non-fasting. One of the SGOT values was within the normal range and all others were elevated. The patient also admitted to ETOH use, possibly accounting for increased LFTs. At his last visit, the patient also had a slightly elevated BUN (29 mg/dL) and uric acid (12.5 mg/dL). All of these adverse laboratory experiences were felt to be probably not drug-related. The ECGs for this patient in the extension phase of the study were essentially the same as in the 03 study. He did experience a T wave change at visit 42 but Dr. Fisch, the consulting cardiologist, noted that that change might be positional. The T wave reading returned to normal on the subsequent ECG and continued to be normal for the rest of the study. The patient was being followed by his internist for diabetes mellitus, hypertension, elevated liver function tests, cholesterol, and triglycerides when his participation in the study ended.

PAR 04-01-022 (Cont.)

On 7/04/86 telephone follow-up revealed that the patient had no withdrawal effects after discontinuing paroxetine and that all adverse clinical experiences had resolved. He was requested to return for repeat laboratory studies on two occasions, but the patient was noncompliant.

On 7/21/86 the patient's wife called the investigator to report that the patient had died in his sleep of a "heart attack" on 7/19/86.

The patient's Certificate of Death listed the immediate cause of death as an acute myocardial infarction with a four-year history of generalized arteriosclerosis as an underlying cause. The death certificate listed diabetes mellitus as a significant condition-contributing to death but not related to the cause of death.

Narrative Summaries of Deaths Reported in
Non-U.S. Clinical Trials

BELGIAN OPEN - 2206.005

PAROXETINE

Patient 605 Female Aged 58 years

Serious adverse event - suicide

Flagged vital signs - standing diastolic BP

This patient successfully completed the short-term phase of the study. During the short-term phase she experienced mild lightheadedness, moderate drowsiness and mild malaise. The investigator considered the lightheadedness and drowsiness to be related to study medication. All these symptoms resolved without treatment.

During the long-term phase of the study the patient's standing diastolic blood pressure attracted a double-flag on day 174 at 40 mm Hg. The standing diastolic reading on day 139 had been 70 mm Hg. The reason for this fall in diastolic blood pressure is unknown.

No adverse events were reported during the first 4 months of long-term therapy but during the first week of the fifth month the patient committed suicide by hanging. No further information is available.

MDUK - 1.13.126

PAROXETINE

Patient 126 Male Aged 50 years

Serious adverse event - death

This patient presented with a 15 month history of untreated depression. There was no previous history of affective disorder.

An initial assessment he was noted to be very apprehensive with slight Rombergism. He suffered from renal calculi and had lost 1.75 stones in weight in 18 months.

Aspirin as required was the only concurrent medication initiated during the study.

There were no double-flagged vital signs.

A raised monocyte count of 14% on day 49 attracted a single-flag. The cause of this was unknown.

The patient experienced severe nausea, dry mouth, and swelling of the right ankle. All these events were considered by the investigator to be related to study medication. The patient also suffered severe tremor of unknown etiology. All these adverse events resolved without treatment.

No adverse events were reported during the first month of long-term treatment. After 2 months the patient complained of severe insomnia, successfully treated with nitrazepam, and moderate paraesthesia which also resolved. Both events were of unknown etiology.

There were no flagged vital signs or laboratory data recorded during the long-term phase of study.

On day 144, after 3 months of long-term therapy, the patient died by hanging. No further information is available regarding this event.

HP/82/47 - 6.47.003

PAROXETINE

Patient 3 Female Aged 56

Reason for safety summary: patient died during study (suicide on day 47). Subject dosing history during study was as follows: Day -7 to -1, placebo od po; Day 1 to 2, paroxetine 10 mg od po; Day 3 to 6, paroxetine 20 mg od po; Day 7 to 47, paroxetine 30 mg od po.

Concomitant medication was isosorbide dinitrate, 15 mg po daily; and metoprolol tartrate, 300 mg po daily. Both drugs continued throughout study.

Concomitant disease: Myocardial infarction 4 years previously.

Clinical interpretation: This patient committed suicide by drowning on day 47 of the study period during treatment with active medication. Her clinical state, as measured by the Hamilton Depression Rating Scale, had improved during the course of the trial, potentially giving her the volition to kill herself. It is known that 15% of patients with depressive illness die by suicide.

PAROXETINE

2406.149

Patient 149 s i F Aged 18

This 18-year-old female had no concurrent illness and was not receiving concurrent medication at baseline.

She experienced a mild dry mouth, which the investigator considered to be drug related, from day 5 for 25 days and a mild eye disorder of unknown relationship to therapy.

The patient received diazepam from day 32 because of increasing restlessness (agitation), and on day 38 she stopped paroxetine treatment and left the clinic. On day 44 the patient committed suicide by overdosage. No further details were available.

The patient had no double-flagged laboratory or vital signs data.

DFG124

PAROXETINE

Patient 12 i 7124-012 F Aged 42 years

This 42 year old female had been depressed for 16 weeks. She had experienced four other episodes of depression in the previous ten years and had been treated with clomipramine, mianserin, and maprotiline; only the third gave a satisfactory response. For the current episode of depression, she had received alprazolam 75 mg daily for three weeks, clomipramine 300 mg daily, and thioridazine 150 mg daily for one week, and she had been taking diazepam 150 mg daily for 12 months. She also took diazepam (dose unspecified) from day -3 to day -2 and chloral hydrate from day -3 to day 8.

She experienced mild hyperkinesia from day 6 which the investigator considered to be unrelated to therapy.

On day 10 the patient committed suicide by over-dosing with doxepin. The relationship of this event to paroxetine therapy was unknown.

No abnormal vital signs or laboratory data were recorded during the study.

Study 6.1.1.1, Boerup C. et al.

Patient 6.1.1.1.15

710-1-015

PAROXETINE

Initials: Redacted Female Aged 71

Event: Patient died April 24, 1980

Paroxetine treatment period: May 29, 1978 to April 20, 1980 (according to case report form)

Summary: Patient Redacted born December 6, 1902, treated with paroxetine 20 mg daily form 5/29/78 to 4/20/80 deceased 4/20/80. In addition to the treatment of her severe manic-depressive mood disorder and dementia initiated 1973, the patient was also in treatment for arteriosclerotic cardiac disease. In the trial period, no unwanted effects were recorded and lab tests of hepatic and renal functions and hematological evaluation showed no abnormal values. Cause of death is most probably lung embolism (evaluated on the basis of ECG), and death certificate was completed at the [redacted] emergency ward.

There were no other adverse events, no changes in laboratory parameters or vital signs.

The global evaluation of side effects indicates that no side effects were present during paroxetine treatment.

It is concluded that paroxetine treatment which was unproblematic cannot reasonably be associated with the death.

On 9/13/78 and 9/2/79, the patient's ESR value rose to 31 and 36 mm/hr respectively. On both occasions the value had returned to normal at the next assessment. Such values would not be considered to be abnormal for a patient of this age but the values do satisfy the safety criteria agreed with the FDA.

SOUTH AFRICAN OPEN

4.02.010

PAROXETINE

Patient No: 10 Female Aged 55 years

Serious adverse event – death

This patient successfully completed the short-term phase of the study.

No abnormal vital signs or laboratory data were recorded during the long-term phase of the study.

On day 56 the patient reported weight gain but this is not substantiated by the weights recorded during the study. She weighted 53 kg at baseline and only increased to 54.2 an day 87. At the same time the patient also reported loss of libido. The investigator was unable to attribute these events to study drug but the dose was reduced.

During the 8th month of therapy the patient reported unpleasant dreams which led to a further reduction in dose.

During the 12th month of long-term therapy, she was tragically murdered.

MDUK26

1.26.34

PAROXETINE

Patient 34 Female Aged 79 years

Serious adverse event - death

This patient successfully completed the short term phase of the study with no double flagged vital signs or laboratory data, just a slight increase in weight.

During long term treatment the patient reported a loss of energy but there is very little information with respect to this .

The patient was suspected of having cancer when she entered the study and during the fourth month she died of liver metastases from bowel cancer. Death was considered unrelated to paroxetine treatment.

No double flagged vital signs were recorded during the long term phase of the study and no laboratory data was collected.

MDUK13P

1.13.028

PAROXETINE

Patient 28 Male Aged 60 years

Serious adverse event - death

This patient presented with a 4 month exacerbation of intermittent depression and anxiety which had lasted for 4 years. He had been taking amitriptyline 75mg daily for 18 months. This was stopped on day -7. He had previously shown a poor response to mianserin 30mg daily and nitrazepam.

He had a history of nocturnal cramps and a congenital abnormality of his left eye. At baseline he was taking oxerutin 250mg daily. This was continued throughout the study period at a dose of 500mg. There were no double-flagged vital signs or laboratory data.

During the short-term phase of the study, he experienced moderate nausea which was not considered related to study medication and resolved after 2 days.

He entered the long-term phase of the study and experienced no adverse events for the first month. No further laboratory data were generated and his vital signs after the first month were unremarkable.

The patient died suddenly during the second month of the long-term treatment following several episodes of chest pain. His family refused permission for a post-mortem examination and death was presumed due to myocardial infarction. A tablet count revealed no evidence of overdose of study medication. It was considered by the investigator that there was no evidence to relate death to paroxetine in either the recommended or excessive dosage.

2113-003

PAROXETINE

Patient 003 Female Aged 74 years

This 74-year-old female patient presented with sclerotic myocardiopathy and diabetes mellitus. She was stabilized on glibenclamide and digoxin, which were continued for the study period.

The patient died on day 13 of the study having suffered a pulmonary embolism. The investigator did not feel this adverse event was drug related.

117A-004

PAROXETINE

Patient 4 Male Aged 84 years

This patient had ischaemic heart disease with elevated levels of CPK and HBDH on day -24. On day -34 an ECG showed a bundle branch block and an irregular pulse on day -10 indicated atrial fibrillation. He also had a hiatus hernia, and bronchial asthma. The latter was thought to be possibly psychogenic. The patient was receiving digoxin and an antacid.

On day 3 this patient attempted to slash his wrists and abdomen and was withdrawn from the study. The investigator described the event as a "feeble suicidal gesture" to avoid being transferred to another hospital. Four days after stopping paroxetine therapy the patient died. An autopsy determined cause of death as coronary atherosclerosis.

6.67.002

AMITRIPTYLINE

Patient 2, HP/83/67, Male, Age 36.

Reason for safety summary: patient died after week 7 visit of study (committed suicide).

Subject dosing history during the study:

Day -7 to 0 - placebo od po
Day 1 to 42 - amitriptyline 150mg od po

Concomitant Medication:

None reported

Concomitant Disease:

None reported

Clinical Interpretation:

This patient committed suicide after the week 7 visit. It is known that 15% of patients with depressive illness die by suicide and his death is unlikely to be drug related.

His clinical condition had actually improved during the trial and, as is often the case, this may have given the patient the volition to kill himself.

237I.054

CLOMIPRAMINE

Patient 54 i Male Aged 66 years

The patient was a 66-year-old male with depression for 3 months. There had been one previous episode. Long term usage of nitrazepam, 1 tablet daily, was stopped on day 8. He had mild psychomotor retardation for the first 5 week or treatment; this disappeared before the end of the study and was regarded by the investigator as probably related to therapy. Having completed the 6 weeks of the trial, he was then changed to fluvoxamine but one month later he committed suicide by hanging.

7124.023

IMIPRAMINE

Patient 23 i Male Aged 58 years

This 58 year old male had a 12-week history of depression which had been treated with doxepin 150 mg daily for five weeks and maprotiline 150 mg for four weeks. He received oxazepam 50 mg daily from day -2 and this was continued throughout the study.

He started acebutolol 200 mg daily from day 11 and ketoprofen 150 mg daily from day 14.

The patient had no double flagged vital signs or laboratory data.

The patient experienced moderate impairment of urination and dry mouth, probably related to imipramine, moderate amnesia and mild paraesthesia, possibly related to imipramine, from day 8. He also showed a lack of emotion which the investigator considered to be unrelated to imipramine. The patient experienced mild somnolence, possibly related to imipramine, from day 15.

The patient committed suicide by shooting on day 18. The relationship of this event to imipramine therapy is unknown.

7119.009

PLACEBO

Patient 9 Male Aged 49 years

This 49 year old male patient received oxazepam from day 2. He did not have any concurrent illness at baseline or during the study.

The patient committed suicide during the placebo run-in phase.

No vital signs or laboratory data were recorded during the study.

7119.062

PLACEBO

Patient 62 Male Aged 43 years

This 43 year old male patient had previously received amoxapin to treat the present episode of depression which had lasted for 20 weeks. He did not have any concurrent illness or concomitant medication at baseline or during the study.

The patient committed suicide during the placebo run-in phase of the study.

There were no double flagged vital signs or laboratory data recorded during the study.

11. SUICIDE ATTEMPTS

U.S. Clinical Trials

A total of 14 suicide attempts were reported in the U.S. clinical trial program. In no case was the patient successful. An overview of the U.S. data is presented in the table below.

Table XI.19
Overview of Attempted Suicide - U.S. Data

	PAROXETINE N=1562	PLACEBO N=497	OTHER A.D. N=464
DRUG OVERDOSE (imipramine)	9	0	1
DEFENESTRATION	2	0	0
SELF-INFLICTED INJURY	1	0	0
SUFFOCATION	0	1	0
TOTAL	12(0.77%)	1(0.20%)	1(0.21%)

Clinical summaries of the suicide attempts reported in U.S. trials follow this section. An overview of the characteristics of attempted suicide patients in the U.S. program is shown in Table XI.20.

Table XI.20
Overall Characteristics of Attempted Suicides - U.S. Data

P.I.D.	Sex	Age	Prescribed Dosage (mg/day)	Duration (Days)	Description
PAROXETINE					
02-04-089	F	19	20	40	150 - 200 mg - recovered
04-01-009	M	26	50	225	850 mg - semi-obtunded, improved without sequelae
04-02-056	M	56	40	20	Self - inflicted lacerations, recovered
04-06-096	M	34	30	116	Dalmane + ETOH, recovered
05-01A-030	F	23	40	35	Two attempts with paroxetine-no ill effects
05-01A-075	F	37	50	>3yrs.	300 mg - N & V in ER, Rec.
05-02B-019	F	30	50	57	Pill O.D. pb. not paroxetine, recovered
05-02F-002	F	39	40	38	NYTOL + ETOH, recovered
07-01A-001	M	25	40	20	Attempted defenestration, no injuries
09-01A-005	F	35	40	7	400mg + other meds, obtunded, recovered
09-01E-260	F	52	10	60	ETOH, detoxified
09-01J-573	M	43	10	26	Defenestration, multiple fractures
IMIPRAMINE					
04-06-088	M	37	225	61	ETOH + pills, recovered
PLACEBO					
02-01-009	F	67	-	6	Attempted suffocation, deterred

No pattern in age, sex, dose of paroxetine, or duration of paroxetine treatment is predictive of suicide risk.

The worldwide data for attempted suicides and overdoses is shown in the following table.

Table XI.21

Attempted Suicides and Overdoses - Worldwide Data

	U.S. DATA			NON-U.S. DATA			WORLDWIDE		
	Paroxetine N=1562	Other AD N=464	Placebo N=497	Paroxetine N=1401	Other AD. N=687	Placebo N=57	Paroxetine N=2963	Other AD N=1151	Placebo N=554
Attempted Suicides (%)	12(0.7%)	1(0.2%)	1(0.2%)	30(2%)	13(1.9%)	2*	42(1.4%)	14(1.2%)	3*
Drug Overdose (%)	9(0.6%)	1(0.2%)	0	20(1.4%)	7(1%)	2*	29(1%)	8(0.7%)	2*

* 2 overdoses during placebo run-in period

The rates for attempted suicide and drug overdose (the most common subpopulation of attempted suicides) are not dissimilar when paroxetine is compared to other antidepressants. The data in this table is not adjusted for dose-exposure.

Summaries of Suicide Attempts in U.S. Clinical Trials

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

Patient I.D.	Code	Adverse Experience	Action	PT
02-04-089	ABHXX	Overdose	4	Overdose

The patient is a 19-year-old female with a diagnosis of major depression, recurrent (DSM III 296.3), with no previous psychiatric treatment. The patient was on paroxetine therapy for 40 days (3/9/87 to 4/24/87) taking 20 mg daily. The patient was on no concomitant medication. The patient completed day 28 of the study with HAMD total of 11. On 4/24/87, the patient called the study site and related that she had taken 15 to 20 capsules (150-200 mg) of paroxetine (out of anger, due to an argument with her husband). She related that she continued on her job immediately after taking the capsules and related that she was not experiencing any side effects. The blind was broken by Beecham on 4/24/87; the patient was on paroxetine. The patient did not return to the clinic for final safety assessments. In a phone contact by the site on 5/5/87, the patient reported that she was doing well. A 15-day Drug Experience Report was filed with the FDA by Beecham on 5/5/87.

04-01-009	JDNQC	Suicide Attempt	4	Emotional Lability
	ABHXX	Intentional Overdose	4	Overdose

The patient is a 26-year-old male with a diagnosis of major depression, recurrent (DSM III 296.33). The patient has a long history of major affective disorder with a suicide attempt at age 18 (hospitalization not required). The study screen visit history includes ten years of crying spells and suicidal thoughts, but no attempts. The patient was on paroxetine therapy for 225 days (6/27/85 to 1/5/86); the dose prior to termination was 50 mg daily. The patient had been improving on paroxetine but moved and left his medication behind. He was without medication for 17 days and became increasingly depressed. On 1/5/86, the patient took 153 capsules (17 day supply) of which 5/9, 850 mg, were paroxetine. The patient vomited after the attempt. He was then taken to the emergency room, was lavaged, and admitted to I.C.U. Physical examination revealed the patient to be semi-obtunded but easily arousable within two hours. The mental status exam revealed underactive, motor behavior, increased latency and decreased duration of responses, depressed affect without suicidal thoughts. Further physical alcohol profile was done on 1/5/86; all results were negative. Plasma levels were obtained. The blind was broken by the investigator on 1/5/86; the patient was on paroxetine. The patient was placed on MERITAL 50 mg, bid, and discharged from the hospital on 1/10/86 in improved condition. A 1639 worksheet was completed for this patient.

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

Patient I.D.	Code	Adverse Experience	Action	PT
04-06-096	JDNQC	Suicide Attempt	1	Emotional Lability

The patient is a 34-year-old male with a diagnosis of major depression. The patient was on paroxetine therapy for 116 days (the patient was on placebo in Protocol 03); the dose at termination was 30 mg daily. The patient was on HYGROTON 100 mg daily for mild hypertension. The investigator suspected alcohol and drug abuse by the patient. A urine drug screen done on day 113 showed positive for benzodiazedine metabolites. The patient was contacted on day 118 (8/19/86) and instructed to stop study medication. By patient report, a suicide attempt was made on 9/1/86 by overdose on DALMANE and alcohol. The patient went to the emergency room and was released the same day. The patient denies taking any study medication in suicide attempt. The patient came in to the clinic on day 135 (9.5.86) for final safety assessments. Liver function tests had been elevated beginning 8/14/86 and continued to be elevated on 9/5/86. A follow-up lab was done on 9/13/86; at that time, liver function values were returning to normal. Hospital records were requested by the site, but not received. A 1639 worksheet was completed for this patient.

05-01A-030	ABHXX	Attempted Overdose	4	Overdose

The patient is a 23-year-old female with a diagnosis of major depression, recurrent (DSM III 296.3). She received outpatient psychiatric treatment for four months at age 12. She was on no concomitant medication. The patient was on paroxetine therapy for 35 days (12/20/85 to 1/14/86); the dose at premature termination was 40 mg. On 1/6/86, the patient experienced a situational crisis and reported taking between 120 to 140 mg of paroxetine. She had no ill effects at all. On 1/8/86, 50 capsules (500 mg) were dispensed to the patient. The patient overdosed again on 1/12/86, taking all remaining paroxetine capsules (400 mg); she had no apparent adverse experiences. Subsequent to taking the capsules, she did some excessive drinking. Her behavior became unpredictable and violent and she was admitted to the hospital on 1/14/86. Laboratory tests and ECG were normal. After a brief stay, the patient was discharged from the hospital in satisfactory condition. The patient continued to be followed by the site until 2/3/86.

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

Patient I.D.	Code	Adverse Experience	Action	PT
05-01A-075	ABHXX	Overdose	4	Overdose

The patient is a 37-year-old female with a diagnosis of major depression, recurrent (DSM III 296.3). The patient began paroxetine on 10/25/86 and entered the third year of the study on 10/28/88. On 3/8/89, the patient ingested 300 mg of paroxetine in a suicide attempt; she was seen in the emergency room (psychological loss and situational stress were precipitators of the event). Patient experienced some nausea within the first two hours and vomited a small amount; she also experienced headache. There were no other noticeable adverse reactions. Activated charcoal was administered and she was admitted to the intensive care unit overnight at which time her vital signs were stable and she had no additional adverse experiences. The patient was transferred to the psychiatric unit the following day. Safety tests were performed (physical exam, ECG, laboratory studies) revealing nothing significant. The patient was discharged from the hospital on 3/19/89. No other adverse experiences were reported during the third year of the study and no concomitant medications were taken during this period. Patient was discontinued from the study and medication was stopped on 3/8/89.

05-02B-019	JDNQC	Overdose of Pills (Suicide Attempt)	4	Emotional Lability

The patient is a 30-year-old female with a diagnosis of major depression, recurrent (DSM III 296.3). The patient was first treated for psychiatric illness at age 28, outpatient treatment only. The patient was on paroxetine therapy for 57 days (3/5/87 to 4/30/87). The dose at termination was 50 mg daily. On 5/5/87, the site was notified by the patient's relative that the patient had taken an overdose of 20 to 50 pills of unknown origin. The patient was taken to the emergency room and was hospitalized from 5/8/87 to 5/10/87. Hospital records were not obtained. The investigator felt that the overdose medication was not paroxetine. The Drug Accountability record adds confirmation to this; the patient returned more medication than she should have after having allegedly overdosed. The patient returned to the clinic on 5/12/87 for final assessments; laboratory work and ECG were normal. A Drug Experience report was filed with the FDA on 7/31/87.

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

Patient I.D.	Code	Adverse Experience	Action	PT
05-02F-002	ABHXX	Overdose	4	Overdose

The patient is a 39-year-old female with a diagnosis of major depression, recurrent (DSM III 296.3). The patient's psychiatric history includes 12 months outpatient treatment at age 16 and one subsequent hospitalization for 3 months. The patient was on no concomitant medications. The patient was on paroxetine therapy for 38 days; the dose at termination was 40 mg daily. The patient had not been responding to paroxetine (HAMD on 1/12/87 = 20). On 1/24/87, the patient attempted suicide by ingesting 32 tablets of NYTOL (diphenhydramine hydrocloride) and 3 12 oz. cans of beer. The patient was taken to the hospital where gastric sequelae were noted. The patient stated that she did not take paroxetine capsules in the suicide attempt. Bospital laboratory tests and ECG were normal. Plasma samples were taken for paroxetine assay. The patient was hospitalized for one week. A Drug Experience report was filed for this patient with the FDA on 2/4/87. The site had follow-up contact with the patient by phone on 6/2/87. She continued to exhibit depressive symptoms but has had no further suicide attempts; she is working and functioning effectively.

09-01A-005	ABHXX	Overdose	1	Overdose

The patient is a 35-year-old female with a diagnosis of major depression, recurrent (DSM III 296.33). The patient first received psychiatric treatment at age 33 (16 months of outpatient treatment); she had one 3-week hospitalization. The patient was on paroxetine therapy 40 mg daily for 7 days (5/23/85 to 5/29/85). She was terminated prematurely from the study due to adverse experiences of nausea, drowsiness, and tremulousness. On 6/5/85, the patient was seen in the emergency room after ingesting 9-10 paroxetine capsules (360 - 400 mg). The patient was obtunded at time of admission (2:00 a.m.) but was alert by 9:00 a.m. Coma panel revealed the presence of methocarbamol and phenylpropanolamine in the urine. Testing was not done for paroxetine. There were no laboratory or ECG changes. The patient was admitted to the hospital (psychiatric unit). She was placed on trazodone 200 mg daily and discharged from the hospital on 7/20/85 in improved condition. A 1639 worksheet was completed for this patient.

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Imipramine

Patient I.D.	Code	Adverse Experience	Action	PT
04-06-088	JINQC	Attempted Suicide	4	Emotional Lability

The patient is a 37-year-old male with a diagnosis of major depression, recurrent (DSM III 296.3). The patient was on no concomitant medication. The patient continued on imipramine from Protocol 03 to Protocol 04. The duration on imipramine was 61 days (3/27/86 to 5/26/86); the dose at termination was 225 mg daily. On 5/26/86, the patient was hospitalized for a possible suicide attempt. The patient had been dispensed 279 capsules of study medication 18 days prior to hospitalization. The patient took an unknown quantity of capsules and was intoxicated. The blind was broken by the investigator (the patient was on imipramine) and the information was provided to the treating physician. On 5/28/86, the patient was contacted by telephone at his home by the site. He reported that he was "doing fine." The patient refused to return to the clinic for follow-up; the site was unable to obtain the hospital records. A 1639 worksheet was completed for this patient.

SUICIDE ATTEMPT: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

Patient I.D.	Code	Adverse Experience	Action	PT
04-02-056		Suicide Attempt		Suicide Gesture

The patient is a 56-year-old male with a diagnosis of major depression, single episode, without melancholia (DSM III 296.22). The patient completed Protocol 03 (placebo) and crossed over to paroxetine therapy on 5/7/86. Dry mouth was the only adverse experience reported during the study. On 5/26/86, the patient was admitted to the V.A. Hospital Psychiatric Unit due to self-inflicted scratches to his throat and both wrists. The blind was broken by the investigator on 5/29/86 (the patient was on paroxetine). The patient was discontinued from the study on 5/26/86 due to lack of efficacy (20 days of paroxetine therapy). While hospitalized, the patient received seven ECT treatments between 7/23/86 and 8/11/86 and showed improvement. After 8/11/86, he failed to return from a hospital weekend pass, and was found to have moved from his last known address; he was lost to follow-up. A 1639 worksheet was completed (but not filed with the FDA) for this patient.

07-01A-001	Suicide Attempt	1	

The patient is a 25-year-old male with a diagnosis of major depressive disorder, unipolar, recurrent with melancholia (DSM III 296.33). Concomitant medications: chloralhydrate 500 mg hs (on 11/1/86) for sleep and TYLENOL 10 grains (on 11/14/86) for headache. The patient was on paroxetine therapy from 11/1/86 to 11/19/86; dose at study termination was 40 mg. The patient was hospitalized on 10/27/86 for evaluation and treatment of his depressive episode (this protocol is inpatient study). The patient showed improvement and was discharged on 11/15/86 on paroxetine 40 mg/day. The patient did not take medication on 11/16/86 and 11/17/86; lack of compliance. Patient was rehospitalized on 11/18/86 due to acute depression symptoms and suicidal ideations (patient attempted to jump from a bridge). Patient was discontinued from the study and medication was stopped on 11/19/86 due to lack of efficacy. Patient was discharged from the hospital on 11/28/86, on ELAVIL 150 mg and TRILAFON which required hospitalization from 1/2/87 to 1/6/87. The patient showed progressive improvement and was doing well as of 2/23/87.

SUICIDE ATTEMPT: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

Patient I.D.	Code	Adverse Experience	Action	PT
09-01E-260	JINQC	Suicide Attempt	3	Emotional Lability

The patient is a 52-year-old female with Axis I diagnosis of major depression, recurrent (DSM III 296.3) and alcohol dependency, continuous (DSM III 303.91) and Axis II diagnosis of mixed personality disorder (DSM III 301.89). The patient's medical history includes 5 nasal surgeries since 1979, Meniere's syndrome, and ear surgery in March 1985. The patient completed the study on paroxetine with an eight day dose interruption (during hospitalization). The patient was on 10 mg of paroxetine daily. The patient was admitted to the hospital on 8/28/85 for detoxification. She had been drinking heavily due to situational stressors. Upon admission, her blood alcohol level was 0.182; other lab studies were normal. The mental status exam revealed the patient to be alert with no major thought disorder; she was depressed but denied suicidal thoughts. Hospital records were obtained. A 1639 worksheet was not completed for this patient. The patient was discharged from the hospital on 9/15/85 and was to attend a chemical addiction clinic as an outpatient.

09-01J-573	JINQC	Attempted Suicide	4	Emotional Lability

The patient is a 43-year-old male with major depression, recurrent (DSM III 296.3). The patient was first treated for psychiatric illness at age 31; history includes 2 months' outpatient treatment and one hospitalization for 2 weeks. The patient is blind in both eyes (since birth). He was on no concomitant medication. The patient was on paroxetine therapy 10 mg daily for 26 days (6/29/85 to 7/24/85). The patient was responding to paroxetine; on 7/19/85 (day 21) the HAMD was 12. The patient reported stopping his medication on approximately 7/24/85 because his mood was better. On 7/29/85, the patient attempted suicide by jumping two floors off a building. The patient reports that the reason was because of being "hounded" by his creditors. The patient was hospitalized with multiple fractures; no other adverse experiences were reported. The patient did not return for follow-up visit.

SUICIDE ATTEMPT: U.S. PAROXETINE TRIALS

Treatment Group: Placebo

Patient I.D.	Code	Adverse Experience	Action	PT
02-01-009		Suicide Attempt		Suicide Attempt

The patient is a 67-year-old female with a diagnosis of major depressive disorder, recurrent with melancholia (DSM III 296.33). The patient began placebo on 6/19/85. On 6/25/85, the patient made a suicide gesture by suffocation. Her husband prevented her suicide; she was brought to the investigator the same day. The blind was broken by the investigator on 6/25/85 (placebo); she was discontinued from the study due to lack of efficacy. Poststudy follow-up visit on 6/26/85 revealed her condition continued to deteriorate.

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12. MANAGEMENT OF PAROXETINE OVERDOSE

a. U.S. Data

Paroxetine overdose has not been associated with characteristic physical manifestations found with tricyclic antidepressant overdoses (such as cardiac arrhythmia, coma, seizures, etc.). Management of paroxetine overdose should follow standard clinical practice in treatment of sedative drug overdose. Five paroxetine overdoses were reported in U.S. clinical trials. In two of the overdoses, specific intervention was attempted with a successful outcome. Patient 04-01-009 had gastric lavage and patient 05-01A-075 was given activated charcoal. Patient 09-01A-005 was observed in the emergency room, then admitted to the hospital psychiatric unit for treatment. Patient 05-01A-030 ingested paroxetine twice; the first incidence with no ill effects, the second incidence combined paroxetine with alcohol and was hospitalized. Patient 02-04-089 ingested small amounts of paroxetine with no ill effects. Clinical summaries for these five patients are included after this section. Paroxetine was not associated with any unusual toxicity when taken in overdose.

b Non-U.S. Data

As in the U.S. clinical trial program, cases reported in non-U.S. studies have been associated with a benign outcome. Based on the non-U.S. clinical trial experience, a table of the characteristics and management of paroxetine overdose has been generated which supports the safety of paroxetine in attempted overdoses. These data are presented in Table XI.22.

Table XI.22

MANAGEMENT AND CHARACTERISTICS OF ATTEMPTED OVERDOSE

PAROXETINE ALONE

DOSE	ACTION TAKEN	AERs	OUTCOME
28 x 15mg	Hospitalization Stomach washout	Dilated pupils Dry mouth Sinus tachycardia	Uncomplicated recovery
12 x 30mg	No details	None reported	Full recovery
8 x 15mg	Hospitalization	None reported	Full recovery
2 x 30mg	None	Abnormality of accommodation	Full recovery

PAROXETINE AND OTHER DRUGS

DOSE	ACTION TAKEN	AERs	OUTCOME
5 x 15mg paroxetine +2 x 0.5mg lorazepam	Hospitalization	None reported	Full recovery
120mg paroxetine 250mg nitrazepam 12.5mg hexobabitol	Hospitalization	None reported	Full recovery
6 x 30mg paroxetine +4 pints lager	None	Dizziness, bloated, nauseated, no appetite	Full recovery
Paroxetine & alcohol; dose unknown	Hospitalization	None reported	Full recovery
7 x 30mg paroxetine +3 cans lager	None	Nausea, tiredness, depersonalisation for 24 hours	Full recovery

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

PID	Code	Adverse Experience	Action	PT
04-01-009	JDNQC	Suicide Attempt	4	Emotional Lability
	ABHXX	Intentional Overdose	4	Overdose

The patient is a 26-year-old male with a diagnosis of major depression, recurrent (DSM III 296.33). The patient has a long history of major affective disorder with suicide attempt at age 18 (hospitalization not required). The study screen visit history includes ten years of crying spells and suicidal thoughts, but no attempts. The patient was on paroxetine therapy for 225 days (6/27/85 to 1/5/86); the dose prior to termination was 50 mg daily. The patient had been improving on paroxetine but moved and left his medication behind. He was without medication for 17 days and became increasingly depressed. On 1/5/86, the patient took 153 capsules (17 day supply) of which 5/9, 850 mg, were paroxetine. The patient vomited after the attempt. He was then taken to the emergency room, lavaged, and admitted to I.C.U. Physical examination revealed the patient to be semi-obtunded but easily arousable within two hours. The mental status exam revealed underactive motor behavior, increased latency and decreased duration of responses, depressed affect without suicidal thoughts. Further physical alcohol profile was done on 1/5/86; all results were negative. Plasma levels were obtained. The blind was broken by the investigator on 1/5/86; the patient was on paroxetine. The patient was placed on MERITAL 50 mg, bid, and discharged from the hospital on 1/10/86 in improved condition. A 1639 worksheet was completed for this patient.

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

PID	Code	Adverse Experience	Action	PT
05-01A-075	ABHXX	Overdose	4	Overdose

The patient is a 37-year-old female with a diagnosis of major depression, recurrent (DSM III 296.3). The patient began paroxetine on 10/25/86 and entered the third year of study on 10/28/88. On 3/8/89, the patient ingested 300 mg of paroxetine in a suicide attempt; she was seen in the emergency room (psychological loss and situational stress were precipitators of the event). Patient experienced some nausea within the first two hours and vomited a small amount; she also experienced a headache. There were no other noticeable adverse reactions. Activated charcoal was administered and she was admitted to the intensive care unit overnight at which time her vital signs were stable and she had no additional adverse experiences. The patient was transferred to the psychiatric unit the following day. Safety tests were performed (physical exam, ECG, laboratory studies) revealing nothing significant. The patient was discharged from the hospital on 3/19/89. No other adverse experiences were reported during the third year of the study and no concomitant medications were taken during this period. Patient was discontinued from the study and medication was stopped on 3/8/89.

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

PID	Code	Adverse Experience	Action	PT
09-01A-005	ABHXX	Overdose	1	Overdose

The patient is a 35-year-old female with a diagnosis of major depression, recurrent (DSM III 296.33). The patient first received psychiatric treatment at age 33 (16 months of outpatient treatment); she had one 3-week hospitalization. The patient was on paroxetine therapy 40 mg daily for 7 days (5/23/85 to 5/29/85). She was terminated prematurely from the study due to adverse experiences of nausea, drowsiness, and tremulousness. On 6/5/85, the patient was seen in the emergency room after ingesting 9-10 paroxetine capsules (360 - 400 mg). The patient was obtunded at time of admission (2:00 a.m.) but was alert by 9:00 a.m. Coma panel revealed the presence of methocarbomal and phenylpropanolamine in the urine. Testing was not done for paroxetine. There were no laboratory or ECG changes. The patient was admitted to the hospital (psychiatric unit). She was placed on trazodone 200 mg daily and discharged from the hospital on 7/20/85 in improved condition.

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

PID	Code	Adverse Experience	Action	PT
05-01A-030	ABHXX	Attempted Overdose	4	Overdose

The patient is a 23-year-old female with a diagnosis of major depression, recurrent (DSM III 296.3). She received outpatient psychiatric treatment for four months at age 12. She was on no concomitant medication. The patient was on paroxetine therapy for 35 days (12/20/85 to 1/14/86); the dose at premature termination was 40 mg. On 1/6/86, the patient experienced a situational crisis and reported taking between 120 and 140 mg of paroxetine. She had no ill effects at all. On 1/8/86, 50 capsules (500 mg) were dispensed to the patient. The patient overdosed again on 1/12/86, taking all remaining paroxetine capsules (400 mg); she had no apparent adverse experiences. Subsequent to taking the capsules, she did some excessive drinking. Her behavior became unpredictable and violent and she was admitted to the hospital on 1/14/86. Laboratory tests and ECG were normal. After a brief stay, the patient was discharged from the hospital in satisfactory condition. The patient continued to be followed by the site until 2/3/86.

OVERDOSE: U.S. PAROXETINE TRIALS

Treatment Group: Paroxetine

PID	Code	Adverse Experience	Action	PT
02-04-089	ABHXX	Overdose	4	Overdose

The patient is a 19-year-old female with a diagnosis of major depression, recurrent (DSM III 296.3), with no previous psychiatric treatment. The patient was on paroxetine therapy for 40 days (3/9/87 to 4/24/87) taking 20 mg daily. The patient was on no concomitant medication. The patient completed day 28 of the study with HAMD total of 11. On 4/24/87, the patient called the study site and related that she had taken 15 to 20 capsules (150-200 mg) of paroxetine (out of anger, due to an argument with her husband). She related that she continued on her job immediately after taking the capsules and related that she was not experiencing any side effects. The blind was broken by Beecham on 4/24/87; the patient was on paroxetine. The patient did not return to the clinic for final safety assessments. In a phone contact by the site on 5/5/87, the patient reported that she was doing well. A 15-day Drug Experience Report was filed with the FDA by Beecham on 5/5/87.

Table III.A.2 (Cont.)
Comparison of Adverse Experiences Listed By
Preferred Term Within Body System
Intent-to-Treat Population - Worldwide Data
Events Reported in At Least 1% of Paroxetine Patients

Body System	Preferred Term	Paroxetine (N=2963)	Placebo (N=554)
Nervous System			
	Abnormal Dreams	59 (2%)	4 (1%)
	Agitation	115 (4%)	11 (2%)
	Amnesia	34 (1%)	4 (1%)
	Anxiety	146 (5%)	14 (3%)
	CNS Stimulation	110 (4%)	18 (3%)
	Concentration Impaired	77 (3%)	2 (0%)
	Confusion	43 (1%)	4 (1%)
	Depersonalization	27 (1%)	1 (0%)
	Depression	34 (1%)	2 (0%)
	Dizziness	328(11%)	32 (6%)
	Drugged Feeling	37 (1%)	4 (1%)
	Emotional Lability	42 (1%)	2 (0%)
	Insomnia	410(14%)	40 (7%)
	Lack of Emotion	19 (1%)	1 (0%)
	Libido Decreased	94 (3%)	0 (0%)
	Manic Reaction	27 (1%)	2 (0%)
	Myoclonus	45 (2%)	3 (1%)
	Nervousness	109 (4%)	12 (2%)
	Paresthesia	150 (5%)	12 (2%)
	Somnolence	606(20%)	49 (9%)
	Tremor	320(11%)	10 (2%)
	Vertigo	46 (2%)	1 (0%)

Table III.A.4

Comparisons for Adverse Experiences

Number of Patients Whose Dosage was Permanently Stopped

Due to Adverse Experiences

World-Wide Intent-to-Treat Population

Adverse Experience Preferred Term	Paroxetine (n=523)	Placebo (n=[redacted])	All Other (n=258)
Nausea	121* (23%)	6 (21%)	36 (14%)
Somnolence	84 (16%)	4 (14%)	67 (26%)
Insomnia	66 (13%)	3 (10%)	19 (7%)
Headache	65 (12%)	7 (24%)	28 (11%)
Asthenia	60 (11%)	3 (10%)	39 (15%)
Dizziness	47 (9%)	4 (14%)	44 (17%)
Tremor	44 (8%)	2 (7%)	25 (10%)
Diarrhea	36 (7%)	2 (7%)	6 (2%)
Agitation	33 (6%)	4 (14%)	10 (4%)
Sweating	33 (6%)	2 (7%)	23 (9%)
Dry Mouth	32 (6%)	2 (7%)	74 (29%)
Vomiting	30 (6%)	0 (0%)	5 (2%)
Anxiety	29 (6%)	1 (3%)	16 (6%)
Abdominal Pain	26 (5%)	1 (3%)	7 (3%)
Decreased Appetite	24 (5%)	3 (10%)	10 (4%)
Constipation	24 (5%)	3 (10%)	24 (9%)
Weight Gain	19 (4%)	0 (0%)	4 (2%)
Hypertension	18 (3%)	0 (0%)	3 (1%)
Palpitation	17 (3%)	3 (10%)	19 (7%)
Paresthesia	17 (3%)	0 (0%)	18 (7%)
CNS Stimulation	17 (3%)	4 (14%)	15 (6%)
Blurred Vision	17 (3%)	0 (0%)	12 (5%)
Emotional Lability	16 (3%)	0 (0%)	11 (4%)
Abnormal Ejaculation	15 (3%)	0 (0%)	2 (1%)
Confusion	14 (3%)	0 (0%)	13 (5%)
Chest Pain	13 (2%)	0 (0%)	2 (1%)
Manic Reaction	12 (2%)	1 (3%)	11 (4%)
Malaise	11 (2%)	0 (0%)	8 (3%)
Urination Impaired	11 (2%)	0 (0%)	14 (5%)
Tachycardia	10 (2%)	1 (3%)	7 (3%)
Vertigo	6 (1%)	0 (0%)	10 (4%)

* All percentages are with respect to the number of patients in the drug group who discontinued treatment due to adverse experience.

G. DRUG ABUSE

Antidepressants are not generally considered drugs with significant abuse potential. No formal clinical studies have been completed to assess the abuse potential or prospectively evaluate withdrawal symptoms associated with paroxetine. In an attempt to reveiw the clinical trial experience, a "drug abuse cluster" of adverse experience preferred terms were created. Those perferred terms which were located in the data base which might be helpful in addressing this issue included: alcohol abuse, drug dependence, and withdrawal syndrome. Review of the worldwide data base indicates no evidence of drug abuse with paroxetine.

H. MANAGEMENT OF PAROXETINE OVERDOSE

1. U.S. Data

Paroxetine overdose has not been associated with characteristic physical manifestations found with tricyclic antidepressant overdoses (such as cardiac arrhythmia, coma, seizures, etc.). Management of paroxetine overdose should follow standard clinical practice in treatment of sedative drug overdose. Five paroxetine overdoses were reported in U.S. clinical trials. In two of the overdoses, specific intervention was attempted with a successful outcome. One patient had gastric lavage and a second patient was given activated charcoal. The third patient was observed in the emergency room, then admitted to the hospital psychiatric unit for treatment. A fourth patient ingested paroxetine twice; the first incidence with no ill effects, the second incidence combined paroxetine with alcohol, and the patient was hospitalized. A fifth patient ingested small amounts of paroxetine with no ill effects. Paroxetine was not associated with any unusual toxicity when taken in overdose.