SmithKline Beecham
Pharmaceuticals

December 16, 1999

NDA 20-031 Paxil® (paroxetine hydrochloride) Tablets

Russell Katz, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

General Correspondence: Response to FDA Request for Information

Dear Dr. Katz:

Reference is made to our approved New Drug Applications for Paxil® (paroxetine hydrochloride) Tablets, and Oral Suspension, NDA 20-031, NDA 20-710 respectively. Reference is also made to the FDA letter of April 2, 1999 requesting information on deaths and suicides in randomized, controlled clinical trials for paroxetine in depression.

Further reference is made to my telephone conversation of December 8, 1999 with Dr. Michael Seika in which we discussed updated and additional information regarding the aforementioned request. Specifically, per Dr. Seika's request, the design of the individual studies comprising the database are provided in Attachment 4, in addition, the particular country of origin for each report is now provided in Attachment 2.

As you know, SmithKline Beecham responded to this request on July 13, 1999 with a preliminary assessment of the incidence of deaths and suicides in paroxetine clinical trials in major depression. However, at that time, there were several cases that remained blinded as to double-blind treatment, and it was not clear whether the design of several older studies was double-blind or open-label. Thus, a conservative approach was chosen and all deaths were reported that occurred in double-blind trials and trials where the design was not known. These cases have now been unblinded and open-label studies identified and removed from consideration.

Submitted herein in duplicate, therefore, is SmithKline Beecham's final response to the aforementioned Agency letter. Please refer to Attachment 1 for a review of the 44 deaths occurring in randomized controlled depression trials with paroxetine. Attachment 2 contains a line listing of the individual patient cases. So as to allow an understanding how the 44 cases were arrived at based on the original 59 cases

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989 Telephone (610) 917-7000 Fax (610) 917-7665

addressed in our July 13 response, the latter cases are listed in Attachment 3 with comments as to their final relevance to the FDA request.

Please do not hesitate to contact me at (610) 917-5970 if you have any questions or require additional information.

Sincerely,

Thomas F. Kline
Assistant Director
U.S. Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
SmithKline Beecham Pharmaceuticals	December 16, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(610) 917-5970	(610) 917-7665
APPLICANT ADDRESS *(Number, Street, City, State, County, and ZIP Code or Mail Code and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
1250 S. Collegeville Road P.O. Box 5089 Collegeville, PA 19426	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-031

ESTABLISHED NAME *(e.g., Proper Name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Paxil®	paroxetine hydrochloride

CHEMICAL/BIOCHEMICAL BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
(-) trans-4R-(4'-Flurophenyl)-3S-[3',4' methylenedioxyphenoxy)methyl] piperidine hydrochloride hemihydrate	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	10mg, 20mg, 30mg, 40mg, 50mg	Oral

PROPOSED INDICATIONS FOR USE
Depression, OCD, Panic Disorder, Social Anxiety Disorder

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
General Correspondence

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 2 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether this site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

FORM FDA 356h (7/97) EF

000003

WB 215848

PAR000227817

DX 25-003

This application contains the following items: *(Check all that apply)*		
	1.	Index
	2.	Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3.	Summary (21 CFR 314.50 (c))
	4.	Chemistry section
		A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
		B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
		C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7.	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8.	Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12.	Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13.	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14.	A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15.	Establishment description (21 CFR Part 600, if applicable)
	16.	Debarment certification (FD&C Act 306 (k) (1))
	17.	Field copy certification (21 CFR 314.50 (k) (3))
	18.	User Fee Cover Sheet (Form FDA 3397)
X	19.	OTHER (Specify) General Correspondance: Response to FDA

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by the FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Thomas Kline, Assistant Director U.S. Regulatory Affairs	December 16, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1250 S. Collegeville Road *P.O. Box 5089* *Collegeville, PA 19426*	(610) 917-5970

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FORM FDA 356h (7/97)

000004

WB 215849

PAR000227818

DX 25-004

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Attachment 1

1. Background

To establish the *numerator* of the death incidence, the worldwide AEGIS serious adverse event database was used to identify deaths reported in all randomized controlled trials (RCTs) evaluating either the immediate-release (IR) or controlled-release (CR) formulation of paroxetine. From AEGIS, 131 deaths occurred after randomization and within 30 days of last dose of double-blind paroxetine, placebo or active comparator (all indications). A reporting cut-off date of 17 June 1999 was used. All 131 deaths were reviewed and 93 cases were eliminated where the trial evaluated a primary condition other than depression, the death occurred prior to randomization, or the patient's randomized treatment was active comparator.

In sum, 38 cases were identified that met the above criteria. In addition, 6 additional deaths occurred in the single-blind placebo run-in phase *prior* to randomization and will be discussed separately. All 44 cases are summarized in Attachment 2. When specified by the investigator, death was deemed unrelated or probably unrelated to study medication.

To establish the *denominator* of the death incidence, i.e., the total number of patients exposed to double-blind treatment in paroxetine RCTs in depression, the central database containing centrally-funded paroxetine IR trials was used. As with the AEGIS safety database, the reporting cut-off date for these trials was 17 June 1999. In the central database of depression trials, the total number of patients randomized to either placebo or paroxetine IR is the following:

Paroxetine IR: **5981**[a]
Placebo: **1598**[b]

[a]Excludes 1206 patients from open-label studies, and 29 patients in PMDD study 427.
[b]Excludes 9 patients in PMDD study 427.

The 88 paroxetine IR depression trials in the central database are listed in Attachment 4.

Eighteen of the 38 post-randomization deaths gleaned from AEGIS occurred in the 88 depression trials in the central database. Therefore, knowing the exposure to double-blind treatment across these trials, a death incidence can be determined using these cases (see Table 1 in Section 2 below).

The remaining 20 cases come from trials performed largely by individual country medical departments not included in the central paroxetine database. These 20 deaths are summarized in Section 3.

Ninteen of these 20 cases involve patients randomized to either paroxetine IR or placebo. The incidence of deaths cannot presently be determined using these cases, however, because the total number of patients exposed to paroxetine IR and placebo across local depression studies is not readily available.

The 20th case, which involved a patient randomized to paroxetine CR, *can* be used to determine a death incidence because the total number of patients exposed to paroxetine CR in depression trials in known (see Section 3).

2. Incidence of Deaths in Depression Trials in the Paroxetine Central Database

The 18 post-randomization deaths in the 88 depression RCTs in the central database are organized by treatment as follows (for additional details please refer to the line lisings provided in Attachment 2):

Table 1

Treatment (N)	Non-Suicides n (%)	Suicides n (%)	Total n (%)
Paroxetine IR (5981)	11 (0.18)	6 (0.10)	17 (0.28)
Placebo (1598)	1 (0.06)	0 (0)	1 (0.06)

Thus, 17 out of 5981 (0.28%) patients died after randomization to paroxetine IR or within 30 days of last dose; 6 of these cases are identified as suicides (0.10%).

For patients randomized to placebo, 1 out of 1598 (0.06%) patients died after randomization or within 30 days of last dose; this case was not identified as a suicide.

All but 2 of these 18 cases came from RCTs with an active comparator but no placebo. These 2 cases came from study 083, where one patient taking paroxetine committed suicide (1/172, 0.6%), and one patient taking placebo died from cardiac arrest (1/67, 1.5%).

In addition to these 18 cases, 2 patients died in the placebo run-in phase of the 88 central database trials. Both deaths were due to suicide (see Attachment 2). However, because the number of patients exposed to run-in placebo is not available, the incidence of these suicides cannot be determined.

3. Deaths in Depression Trials Not in the Paroxetine Central Database

The 19 cases involving patients randomized to either paroxetine IR or placebo are summarized below:

Treatment	Non-Suicides	Suicides	Cause of Death Unkown	Total
Paroxetine IR	10[a]	5	0	15
Placebo	2	1	1	4

[a]Total includes one patient in paroxetine CR study 448 who died from myocarditis in the paroxetine IR control group.

The 20th patient, who was randomized to paroxetine CR, died due to heart failure (see Attachment 2). Thus, out of a total number of 212 non-elderly patients in studies 448 and 449 and 104 elderly patients in study 487 treated with paroxetine CR in depression (N=316), the incidence of death on-study or within 30 days of last dose is 1/316 or *0.3%*. None of the 320 patients in these 3 studies taking placebo died.

In addition to these 20 cases, 4 patients died in the placebo *run-in phase* of depression trials not included in the central database. Three of these 4 deaths were due to suicide (see Attachment 2).

Attachment 2

Line Listing of Deaths Occurring On-Drug or Within 30 Days of Last Dose of
Double-blind Paroxetine or Placebo in Depression Trials
Attachment 2

Cutoff = 17 June 1999

AEGIS Case ID	Age (yr)	Sex	Study Drug	Cause of Death	Relationship	Study CPMS# (Original Study Designator)	Reporter's Country	Patient #
Cases from Centrally Databased Paroxetine IR Depression Studies:								
1982900048-1	61	M	Paroxetine IR	MYOCARDIAL INFARCTION	Not Specified	281 [MD/PAR/013028(PHS3/172)]	UK	1 13 028
1986901122-1	50	M	Paroxetine IR	SUICIDE	Not Specified	281 (MDUK/PAR013/3/126)	UK	1 13 126
1987900712-1	42	F	Paroxetine IR	SUICIDE DOXEPIN OVERDOSE	Not Specified	89 (DFG-124)	Denmark	
1988900199-1	56	M	Paroxetine IR	POSSIBLE HEART ATTACK	Unrelated	04 (PAR04-01)	USA	#022
1988902114-1	62	F	Paroxetine IR	SUDDEN DEATH	Not Specified	49	UK	1 49 052
1988902325-1	47	M	Paroxetine IR	DEATH POSS. DUE TO LUNG CANCER	Not Specified	49	UK	1 49 053
1988902384-1	73	F	Paroxetine IR	PULM. EMBOLISM DUE TO DVT	Unrelated	46	UK	046.001.0025
1988902385-1	18	F	Paroxetine IR	SUICIDE	Not Specified	292 (2406)	Germany	2406 149
1988902624-1	66	M	Paroxetine IR	SUICIDE	Unrelated	290 (MDF/29060/III/1727 PAT 54)	France	2371 054
1989901176-1	58	F	Paroxetine IR	SUICIDE BY HANGING	Not Specified	83	Yugoslav.	083.003.1090
1991906366-1	74	M	Paroxetine IR	DEATH, PNEUMONIA	Unrelated	61	Australia	081
1991906513-1	88	F	Paroxetine IR	DEATH, CARDIOGENIC	Unrelated	84	France	084.004.0051
1994000662-1	67	F	Paroxetine IR	SUICIDE	Unrelated	245	Italy	245.161.0163
1994001297-1	83	F	Paroxetine IR	HIP FRACTURE	Unrelated	197	France	197.014.0101
1994004705-1	94	F	Paroxetine IR	HEMORRHAGIC SHOCK	Unrelated	197	France	197.028.0157
1994005858-1	89	F	Paroxetine IR	FEMORAL NECK	Unrelated	197	Austria	197.007.0017
1994006580-1		F	Paroxetine IR	CONGESTIVE HEART FAILURE	Unrelated	197	Germany	197.008.0024
1990900685-1	63	M	placebo	CARDIAC ARREST	Not Specified	83	Yugoslav.	083.002.0020
1999030848-1	49	M	Run-In Placebo	SUICIDE	Not Specified	261 (DFG119)	USA	7119.009
1989900938-1	43	M	Run-In Placebo	SUICIDE	Not Specified	261 (DFG119)	Denmark	7119.062

WB 215855

000010

PAR000227824

DX 25-010

Line Listing of Deaths Occurring On-Drug or Within 30 Days of Last Dose of Double-blind Paroxetine or Placebo in Depression Trials

Attachment 2

Cutoff = 17 June 1999

AEGIS Case ID	Age (yr)	Sex	Study Drug	Cause of Death	Relationship	Study CPMS# (Original Study Designator)	Reporter's Country	Patient #
Cases from Non-Centrally Databased Paroxetine IR Depression Studies:								
1990906535-1	61	M	Paroxetine IR	TUBERCULOSIS	Unrelated	56	UK	94
1991906246-1	63	F	Paroxetine IR	SUICIDE BY DROWNING	Unrelated	97	Denmark	097.001.0923
1992909192-1	81	F	Paroxetine IR	DEATH, POSS. LEFT VENT. FAILURE	Unrelated	103	UK	069
1993000695-1	46	F	Paroxetine IR	SUICIDE	Unrelated	356	Australia	356.006.0092
1994004839-1	32	F	Paroxetine IR	SUICIDE-OVERDOSE	Unrelated	325	Japan	325.017.04202
1994008363-1		M	Paroxetine IR	TUMOR OF CORPUS CALLOSUM	Unrelated	299	UK	299.018.00137
1995005161-1	52	M	Paroxetine IR	ACUTE MYOCARDIAL INFARCT	Prob. Unrelated	332	Belgium	332.011.00190
1996006706-1	41	F	Paroxetine IR	NEOBLASTIC PULMONARY	Unrelated	402	Italy	402.035.00066
1996014025-1	70	F	Paroxetine IR	CEREBRAL HEMORRHAGE	Unrelated	421	Italy	421.021.00472
1996017190-1	86		Paroxetine IR	CARDIOCIRC. COLLAPSE	Unrelated	421	Italy	SE01.016.00033
1997019335-1	79	M	Paroxetine IR	SUDDEN DEATH	Prob. Unrelated	542	USA	542.XXX.00021
1997021348-1	91	F	Paroxetine IR	COMPLICATION POSTSURGERY	Unrelated	421	Italy	421.020.00305
1998024213-1	31	F	Paroxetine IR	SUICIDE	Unrelated	559	USA	
1998030913-1	46	M	Paroxetine IR	SUICIDE	Unrelated	513	USA	513.001.00566
1990900827-1	81	M	Placebo	SUICIDE BY HANGING	Not Specified	97	Denmark	097.001.0703
1991905954-1	69	F	Placebo	DEATH, CAUSE UNKNOWN	Unrelated	97	Denmark	097.001.0705
1996002343-1	70	F	Placebo	SUBDURAL HAEMATOMA	Unrelated	411	Holland	411.025.02514
1997008147-1		M	Placebo	MYOCARDIAL INFARCTION	Not Specified	467	USA	467.XXX.32057
1990905291-1	59	F	Run-In Placebo	SUICIDE BY DROWNING	Not Specified	56	UK	056.022.0051
1990906514-1	75	M	Run-In Placebo	BRONCHOPNEUMONIA	Unrelated	56	UK	109
1992909103-1	53	M	Run-In Placebo	RUPTURED AORTIC ANEURYSM	Unrelated	129	UK	2, Center 2
1995004921-1	63	F	Run-In Placebo	SUSPECTED MYOCARD. INFARCTION	Unrelated	332	UK	332.047.23185
Cases from Non-Centrally Databased Paroxetine CR Depression Studies:								
1996019959-1	19	M	Paroxetine IR	MYOCARDITIS	Unrelated	448	USA	448.021.00280
1997005505-1	69	M	Paroxetine CR	HEART FAILURE	Unrelated	487	USA	487.002.01373

Attachment 3

Attachment 3

Line Listing of

Deaths Occurring On-Drug or Within 30 Days of Last Dose of Study Medication in Paroxetine Depression Trials Submitted to FDA July 13, 1999 (Cut-off 17 June, 1999)

Case ID	Age	Sex	Study Drug	Cause of Death	Relationship	Study	Patient#	Comment
Paroxetine IR Depression Studies:								
1983000398-1	43 Years	Male	BLINDED	-SUICIDE	Not Specified	PAROX/PLAC DFG 119 PAT 62	7119 062	Central Database(Single blind Placebo)
1991905954-1	69 Years	Female	BLINDED	-DEATH, CAUSE UNKNOWN	Unrelated/Not	97	097.001.0705	Local Study- Placebo
1991906246-1	63 Years	Female	BLINDED	-SUICIDE	Unrelated/Not	97	097.001.0923	Local Study-Paroxetine IR
1994004839-1	32 Years	Female	BLINDED	-SUICIDE-OVERDOSE	Unrelated/Not	325	325.XXX.XXXXX	Local Study-Paroxetine IR
1994008363-1		Male	BLINDED	-TUMOUR OF CORPUS	Unrelated/Not	299	299.018.00137	Local Study-Paroxetine IR
1996014025-1	70 Years	Female	BLINDED	-CEREBRAL HEMORRHAGE	Unrelated/Not	421	421.021.00472	Local Study-Paroxetine IR
1996017190-1	86 Years	Unknown	BLINDED	-CARDIOCIRCULATORY	Unrelated/Not	421	SE01.016.00033	Local Study-Paroxetine IR
1997011004-1	65 Years	Male	BLINDED	-SUICIDE	Unrelated/Not	421	421.007.00400	Fluoxetine
1997018025-1	85 Years	Male	BLINDED	-ACUTE PULMONARY	Unrelated/Not	421	421.020.00311	Fluoxetine
1997021348-1	91 Years	Female	BLINDED	-COMPLICATION POST	Unrelated/Not	421	421.020.00305	Local Study-Paroxetine IR
1998030913	46 Years	Male	paroxetine	-SUICIDE		513	513.001.00566	Local Study
1982900048-1	61 Years	Male	paroxetine	-MYOCARDIAL INFARCTION	Not Specified	PHS3/172	Not Specified	Central Database
1986901122-1	50 Years	Male	paroxetine	-SUICIDE	Not Specified	MDUK/PAR013/3/126	1 13 126	Central Database
1986901123-1	60 Years	Male	paroxetine	-MYOCARDIAL INFARCTION	Not Specified	MD/PAR/013-028	1 13 028	Same as 1986900046
1987900712-1	42 Years	Female	paroxetine	SUICIDE-OVERDOSE	Not Specified	Soeborg, Dnmrk		Central Database
1988900199-1	56 Years	Male	paroxetine	-POSSIBLE HEART ATTACK	Unrelated/Not	PAR04-01	#022	Central Database
1988900832-1	75 Years	Female	paroxetine	-LUNG EMBOLUS	Not Specified	MDA/29060/III/3 PAT2	2113 003	Open-label
1988902114-1	62 Years	Female	paroxetine	SUDDEN DEATH	Not Specified	49	1 49 052	Central Database
1988902325-1	47 Years	Male	paroxetine	-DEATH POSS. DUE TO LUNG CANCE	Not Specified	49	1 49 053	Central Database
1988902384-1	73 Years	Female	paroxetine	PULMONARY EMBOLISM DUE TO DV	Unrelated/Not	46	046.001.0025	Central Database
1988902385-1	18 Years	Female	paroxetine	-SUICIDE	Not Specified	PAROX/PAT 149	2406 149	Central Database
1988902624-1	66 Years	Male	paroxetine	-DEATH - SUICIDE	Unrelated/Not	MDF/29060/III/1727 PAT 54	2371 054	Central Database
1989901176-1	58 Years	Female	paroxetine	-SUICIDE	Not Specified	83	083.003.1090	Central Database
1989901201-1	94 Years	Male	paroxetine	-PARASUICIDE	Not Specified	PAROX/29060/111/17A PAT 004	117A 004	Open-label
1989901498-1	71 Years	Female	paroxetine	POSSIBLE LUNG EMBOLISM	Not Specified	6.1.1.1.15	7101 015	Open-label
1990906535-1	71 Years	Male	paroxetine	-TUBERCULOSIS	Unrelated/Not	56	94	Central Study
1991906366-1	74 Years	Male	paroxetine -	-DEATH, PNEUMONIA	Unrelated/Not	61	081	Central Database
1991906513-1	88 Years	Female	paroxetine	-DEATH, CARDIOGENIC	Unrelated/Not	84	084.004.0051	Central Database
1992909192-1	81 Years	Female	paroxetine	-DEATH, POSS. LEFT VENT. FAILURE	Unrelated/Not	103	069	Local Study
1993000695-1	46 Years	Female	paroxetine	-SUICIDE	Unrelated/Not	356	356.006.0092	Local Study

20 cases in Bold are not included among the 44 cases in Attachment 2 because they did not occur during treatment with double-blind paroxetine or placebo

Attachment 3

Line Listing of Deaths Occurring On-Drug or Within 30 Days of Last Dose of Study Medication in Paroxetine Depression Trials

Submitted to FDA July 13, 1999 (Cut-off 17 June, 1999)

Case ID	Age	Sex	Study Drug	Cause of Death	Relationship	Study	Patient#	Comment
Paroxetine IR Depression Studies:						25	Not specified-Japan s	
1993904867-1	24 Years	Male	paroxetine	-POSSIBLE SUICIDE	Unassessed (Not	PMS PARDM2		Open-label
1993905156-1	65 Years	Female	paroxetine	-DEATH DUE TO AN ACCIDENT	Unrelated/Not	PMS PARDMP		Open-label
1993905238-1	60 Years	Female	paroxetine	-DEATH FOLLOWING SURGERY OF H	Unrelated/Not	PMS PARDM2		Open-label
1993905248-1	82 Years	Female	paroxetine	-DEATH, CAUSE UNKNOWN	Unrelated/Not	PMS PARDMO		Open-label
1993905249-1	82 Years	Unknown	paroxetine	-DEATH, CAUSE UNKNOWN	Unrelated/Not	PMS PARDMP		Open-label
1993905268-1	67 Years	Male	paroxetine	-CEREBRAL APOPLEXY	Unrelated/Not	PMS PARDM2		Open-label
1993905412-1	85 Years	Female	paroxetine	-CARDIAC FAILURE	Unrelated/Not	PMS PARDMP		Open-label
1993905485-1	79 Years	Male	paroxetine	-DEATH, CAUSE UNKNOWN	Unrelated/Not	PMS PARDMP		Open-label
1993905566-1		Female	paroxetine	-SUICIDE	Unrelated/Not	PMS PARDMP		Open-label
1993905567-1		Male	paroxetine	-DEATH DUE TO PNEUMONIA	Unrelated/Not	PMS PARDMP		Open-label
1993905604-1	95 Years	Female	paroxetine	-DEATH, NOS	Unrelated/Not	PMS PARDM2		Open-label
1994000662-1	67 Years	Female	paroxetine	-SUICIDE	Unrelated/Not	245	245.161.0163	Central Database
1994001297-1	83 Years	Female	paroxetine	-HIP FRACTURE	Unrelated/Not	197	197.014.0101	Central Database
1994004705-1	94 Years	Female	paroxetine	-HEMORRHAGIC SHOCK	Unrelated/Not	197	197.028.0157	Central Database
1994005858-1	89 Years	Female	paroxetine	-FEMORAL NECK	Unrelated/Not	197	197.007.0017	Central Database
1994006580-1		Female	paroxetine	-CONGESTIVE HEART FAILURE	Unrelated/Not	197	197.008.0024	Central Database
1995004356-1	46 Years	Female	paroxetine	-FATAL MOTOR VEHICLE	Unrelated/Not	PMS D-QUART		Open-label
1995005161-1	52 Years	Male	paroxetine	-ACUTE MYOCARDIAL INFARCT	Probably	332	332.011.00190	Local Study
1995007581-1	80 Years	Male	paroxetine	-CARDIAC ARREST	Unrelated/Not	436	436.00419	Open-label
1995009080-1	67 Years	Male	paroxetine	-SHOCK CARDIOGENIC	Unrelated/Not	PMS DQUART	14143	Open-label
1996006706-1	41 Years	Female	paroxetine	-NEOBLASTIC PULMONARY	Unrelated/Not	402	402.035.00066	Local Study
1997019335-1	79 Years	Male	paroxetine	-SUDDEN DEATH	Probably	542	542.XXX.00021	Local Study
1998024213-1	31 Years	Female	paroxetine	-SUICIDE	Unrelated/Not	559		Local Study
1999000685-1	63 Years	Male	placebo	-CARDIAC ARREST	Not Specified	83	083.002.0020	Central Database
1999000827-1	81 Years	Male	placebo	-COMMITTED SUICIDE BY HANGING	Not Specified	97	097.001.0703	Local Study
1996002343-1	70 Years	Female	placebo	-SUBDURAL HAEMATOMA	Unrelated/Not	411	411.025.02514	Local Study
1997008147-1		Male	placebo	-MYOCARDIAL INFARCTION	Not Specified	467	467.XXX.32057	Local Study
Paroxetine CR Depression Studies:								
1996019959-1	19 Years	Male	paroxetine IR	-MYOCARDITIS	Unrelated/Not	448	448.021.00280	Local Study
1997005505-1	69 Years	Male	paroxetine CR	-HEART FAILURE	Unrelated/Not	487	487.002.01373	Local Study

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Attachment 4

Attachment 4

Double-blind Paroxetine IR Depression Trials in SB Central Database

Cutoff = 17 June 1999

CPMS Study #	PID First 4 Digits	Original Study Name	Paroxetine IR	Placebo	Active Comparator	Total	Design*
		N/Group:	5981	1598	3978	11557	
1	01.0	STUDY 001	25	25	0	50	Phase II/Parallel
2	02.0	STUDY 02.001	168	169	0	337	Phase II/Parallel
3	03.0	STUDY 03.001	240	240	237	717	Parallel
4	04.0	STUDY 004	219	0	79	298	Extension of Study 3
6	06.0	STUDY 006	33	0	32	65	Parallel
7	07.0	STUDY 007	13	12	13	38	Parallel
9	09.0	STUDY 009	409	51	0	460	Parallel
11	11.0	STUDY 011	103	0	103	206	Parallel
19	4 01	MDINT03 GAGIANO COMP	31	0	35	66	Parallel
20	1 20	MDUK20 AKHTAR	24	0	24	48	Parallel
22	1 22	MDUK22 CARLE/PENDER	16	0	17	33	Parallel
25	1 25	MDUK25 ECCLESTONE	4	0	4	8	Parallel
26	1 26	MDUK26 DORMAN	29	0	28	57	Parallel
27	1 27	MDUK27 PEET/GHADVI	16	0	14	30	Parallel
28	1 28	MDUK28 BRAY	13	0	12	25	Parallel
29	1 29	MDUK29 SUD	3	0	4	7	Parallel
30	1 30	MDUK30 SHUR	20	0	16	36	Parallel
32	1 32	MDUK32 BEAUMONT	30	0	30	60	Parallel
35	1 35	MDUK35 TOONE	3	0	3	6	Parallel
38	1 38	MDUK38 CHAKRAVARTI	32	0	29	61	Parallel
43	1 43	MDUK43 WINSLOW	13	0	16	29	Parallel
46	1 46	MDUK46 ADDALA	19	0	22	41	Parallel
47	1 47	STUDY 047	46	0	49	95	Parallel
49	1 49	MDUK49 HUTCHINSON	58	0	32	90	Parallel
57	057.	STUDY 057	131	136	0	267	Parallel
59	059.	STUDY 059	72	0	71	143	Parallel
60	060.	STUDY 060	44	0	47	91	Parallel
61	061.	STUDY 061	54	0	52	106	Parallel
63	063.	STUDY 063	21	0	19	40	Parallel
64	064.	STUDY 064	49	0	50	99	Parallel
65	065.	STUDY 065	28	0	32	60	Parallel
69	069.	STUDY 069	45	0	46	91	Parallel
70	070.	STUDY 070	31	0	29	60	Parallel
71	239A,B,C	MDF 1729, 1730, 1731	9	0	9	18	Parallel
73	073.	STUDY 073	6	0	4	10	Parallel
74	2474, 2475	STUDY 074	20	0	20	40	Parallel
76	076.	STUDY 076	4	4	4	12	Parallel
77	2477/78/79	STUDY 077	15	0	16	31	Parallel
78	078.	STUDY 078	154	0	152	306	Parallel
79	079.	STUDY 079	45	0	45	90	Parallel
80	080.	STUDY 080	10	0	13	23	Parallel
82	082.	STUDY 082	37	0	34	71	Parallel
83	083.	STUDY 083	172	67	0	239	Parallel
84	084.	STUDY 084	6	0	5	11	Parallel
86	086.	STUDY 086	271	0	273	544	Parallel

88	7123	DFG 123 P31	15	0	15	30	Parallel
89	7124	DFG 124 P32	25	0	34	59	Parallel
90	7130	DFG 130 P33	79	0	78	157	Parallel
94	094.	STUDY 094	65	0	0	65	2 Parall. 60mg Regimens
95	095.	STUDY 095	134	0	68	202	Parallel
106	106.	STUDY 106	18	18	0	36	Parallel
112	112.	STUDY 112	55	0	65	120	Parallel
115	115.	STUDY 115	284	118	289	691	Parallel
128	128.	STUDY 128	357	140	351	848	Parallel
131	131.	STUDY 131	102	0	101	203	Parallel
135	135.	STUDY 135	60	0	61	121	Parallel
184	128A	MDUK28A BRAY	5	0	4	9	Parallel
189	189.	STUDY 189	242	0	0	242	Fluoxetine Switch-With/
							Without Fluox. Washout
190	190	Study 190	61	64	0	125	Parall.Relapse Prev.
197	197.	STUDY 197	99	0	99	198	Parallel
201	201.	STUDY 201	57	60	0	117	Parall.Relapse Prev.
245	245.	STUDY 245	500	0	502	1002	Parallel
251	251.	STUDY 251	125	129	0	254	Parallel
256	2216-2219	BELGIUM M/C COMP	39	0	34	73	Parallel
260	7201	61201 L.LAURSEN P41	20	0	20	40	Parallel
261	7119	DFG 119 DUAG P30	60	0	56	116	Parallel
272	1 04	MDUK04 LAVIN	5	0	3	8	Parallel
274	1 06	MDUK06 NAYLOR	22	23	0	45	Parallel
275	1 07	MDUK07 SILVERSTONE	4	3	4	11	Parallel
276	1 09	MDUK09 EDWARDS	20	21	0	41	Parallel
279	1 12	MDUK12 TRIMBLE	21	10	16	47	Parallel
281	1 13	MDUK13 WADE	100	0	97	197	Parallel
289	2321-2326	FRENCH M/C COMP	42	0	43	85	Parallel
290	237C-G,I,J,L	MDF 1727 M/C COMP	40	0	39	79	Parallel
291	238A,B,D-G	MDF 1728 COMP	41	0	42	83	Parallel
292	2401/02/03/06	GERMAN MC COMP	46	0	44	90	Parallel
308	6 74	HP/81/74 LAXENAIRE	10	0	12	22	Phase II/Parallel
309	6162	HP/81/162A BATTEGAY	11	0	10	21	Phase II/Parallel
310	6 85	HP/81/85A VARACKX-HAENE	9	0	10	19	Phase II/Parallel
312	6 67	HP/83/67 MARGO	1	0	2	3	Phase II/Parallel
316	6 47	HP/82/47A VERVARCKE	9	0	8	17	Phase II/Parallel
318	6 64	HP/82/64A GOFFAUX	9	0	12	21	Phase II/Parallel
319	6148	HP/81/148 RICHOU	1	0	1	2	Phase II/Parallel
327	327.	STUDY 327	81	85	0	166	Parallel
329	329	Study 329	93	87	95	275	Parallel
352	352.	STUDY 352	35	43	39	117	Phase IV/Parallel
377	377	Study 377	182	93	0	275	Parallel
?	6134	HP/82/184 JAUNAR	6	0	4	10	Parallel
* All studies were conducted in Phase III except where noted.							