

1. APPENDIX 6

1.1. Narratives for Cases of Suicides in Clinical Trials

Table 1.1 Patient Identifiers of Patients who Completed Suicide during Paroxetine Clinical Trials

Patient Number	Study	Study Treatment
083.003.1090	29060/083	Paroxetine
1 13 126	MDUK 13 Wade	Paroxetine
2206 005	Belgian MC Open	Paroxetine
2406.149	German MC Comparative	Paroxetine
245.161.0163	29060/245	Paroxetine
502.037.05146	29060/502	Paroxetine
6 47 003	HP 82 47a Vervarcke	Paroxetine
650.307.06282	29060/650	Paroxetine
7124.012	DFG 124 P32	Paroxetine
057.012.1217	29060/057	Placebo
627.605.01012	29060/627	Placebo
785.721.00716	29060/785	Placebo
197.045.0322	29060/197	Comparator – Imipramine
2371 054	MDF 1727 MC Comparative	Comparator –Clomipramine
6 67 002	HP 83 67 Margo	Comparator – Amitriptyline
7124 023	DFG 124 P32	Comparator – Imipramine
7124 060	DFG 124 P32	Comparator – Imipramine

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Table 1.2 Study Treatment Start and Stop Dates and Date of Death for Patients who Committed Suicide during Paroxetine Clinical Trials

Patient Number	Study Treatment	Study Type	Study Treatment		Suicide
			Start Date	Stop Date	Date Died
083.003.1090	Paroxetine	Uncontrolled	10 Apr 1989	17 Apr 1989	18 Apr 1989
1 13 126	Paroxetine	Active Cont	28 Feb 1984	19 Jul 1984	20 Jul 1984
2206 005	Paroxetine	Uncontrolled	13 Jul 1985	10 Jan 1986	10 Jan 1986
2406.149	Paroxetine	Active Cont	11 May 1987	17 Jun 1987	24 Jun 1987
245.161.0163	Paroxetine	Active Cont	20 Jan 1994	22 Jan 1994	22 Jan 1994
502.037.05146	Paroxetine	Placebo Cont	10 Jun 1997	14 Jul 1997	14 Jul 1997
6 47 003	Paroxetine	Active Cont	16 Feb 1983	27 Mar 1983	03 Apr 1983
650.307.06282	Paroxetine	Uncontrolled	24 Mar 2000	30 Mar 2000	30 Mar 2000
7124.012	Paroxetine	Active Cont	08 May 1987	16 May 1987	17 May 1987
057.012.1217	Placebo	Placebo Cont	27 Apr 1991	16 Jul 1991	18 Aug 1991
627.605.01012	Placebo	Placebo Cont	13 Feb 1999	01 Mar 1999	18 Mar 1999
785.721.00716	Placebo	Placebo Cont	31 May 2001	10 Jul 2001	29 Jul 2001
197.045.0322	Imipramine	Active Cont	06 Dec 1994	27 Dec 1994	28 Dec 1994
2371 054	Clomipramine	Active Cont	29 May 1987	10 Jul 1987	10 Aug 1987
6 67 002	Amitriptyline	Active Cont	18 Oct 1983	15 Nov 1983	29 Nov 1983
7124 023	Imipramine	Active Cont	13 Feb 1987	02 Mar 1987	02 Mar 1987
7124 060	Imipramine	Active Cont	01 Dec 1987	27 Dec 1987	27 Dec 1987

Patient 083.003.1090

Study Medication: Paroxetine

Cause of Death: Suicide (by hanging)

This 58 year old female had hypertension on entry to the study. She had been receiving metoprolol 100mg daily and amiloride plus hydrochlorothiazide from day -54. She had suffered five or six previous episodes of depression for which she had received treatment with bi/tri/tetracyclic antidepressants and benzodiazepines. The duration of the present episode of depression was recorded as 1 to 3 months. She had received previous treatment for this episode with bi/tri/tetracyclic antidepressants, which were stopped on day -1, and benzodiazepines, which were stopped on day -4.

The patient received 20mg paroxetine from days 0 to 8. She also received temazepam 20mg, twice or three times daily, from day 0, and chloral hydrate 500mg daily from day 1.

The patient experienced a moderately decreased appetite and mild dryness of the mouth from day 2; both events were considered to be probably related to study treatment.

The patient did not have any double flagged changes in vital signs data and only baseline laboratory assessments were performed.

On day 8 the patient committed suicide by hanging (preferred term: emotional lability). The investigator considered this to be unrelated to study treatment.

Patient 1 13 126

Study Medication: Paroxetine

Cause of Death: Suicide (by hanging)

This 50 year old male had been depressed since his wife was last admitted to the Oncology Department just after Christmas 1982. His wife died due to breast cancer on 15 Jan 1983.

His depression was worsened by being made redundant in Dec 1983. Since becoming unemployed he had been very depressed, only slept 3-4 hours per night, and said he wished he developed a fatal illness but would not consider suicide. When the patient was widowed he was left with only one of two sons at home. This son is going abroad to work and the patient was not looking forward to him leaving.

The patient received study treatment (30mg paroxetine) for over 4 months. He was taking Mogadon (nitrazepam) at night to help him sleep. He occasionally used alcohol, and had no history of drug abuse.

On 20 Jul 1984 the patient committed suicide by hanging. He had made no previous suicide attempts. The investigator considered the suicide was not directly related to study medication

Patient 2206 005

Study Medication: Paroxetine

Cause of Death: Death (by hanging)

This patient was a 58 year old female who was diagnosed with depression with psychotic features. She was admitted to hospital on 09 Jul 1985. The duration of the episode on admission was 6 months. She had had two previous episodes and had received amitriptyline and lithium.

Her family history includes a brother who committed suicide (after a bankruptcy) and her mother had a few psychiatric hospitalisations. She had a compulsive personality, could not cope with the difficulties of each day, and felt worthless since the death of her husband in 1984.

She had made a previous suicide attempt shortly before her admission to hospital. The patient returned home from hospital on 22 Nov 1985. She committed suicide on 10 Jan 1986 by hanging herself. She had taken paroxetine 30mg/day for over 4 months.

Patient 2406.149

Study Medication: Paroxetine

Cause of Death: Suicide (overdose)

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.

Patient 245.161.0163

Study Medication: Paroxetine

Cause of Death: Suicide (jumped from window)

The patient was a 67 year old female with no previous episodes of depression. She had had her current episode for approximately 3 months on entry into the study. The patient was started on paroxetine. She was not taking any concomitant medication.

On day 2, the patient committed suicide by throwing herself out of a third floor window. The investigator considered the suicide to be unrelated to study medication

Patient 502.037.05146

Study Medication: Paroxetine

Cause of Death: Suicide (suspected overdose)

Case reference 97017163-1 is a clinical trial report from study 29060/502 which is a double blind study, referring to a male patient aged 23 years.

On the 10 June 1997, the patient started taking study medication for social phobia. He received paroxetine at daily doses of 20mg from 10 Jun 1997 to 23 Jun 1997, 30mg from 24 Jun 1997 to 30 Jun 1997, 40mg from 01 Jul 1997 to 07 Jul 1997, and 50mg from 08 Jul 1997 to 14 Jul 1997. The patient failed to present for a scheduled appointment on 15 July 1997; the investigator was later informed that the patient committed suicide on 14 July 1997.

According to the patient's mother, the patient had stolen a large amount of his grandmother's medication (bisporolol hemifumarate, isosorbide dinitrate, nitrazepam). An autopsy has been refused by the patient's parents.

The investigator considered that the events were probably unrelated to study medication and could possibly be associated with the patient's primary condition

Patient 6 47 003

Study Medication: Paroxetine

Cause of Death: Suicide (by drowning)

This patient was a 56 year old female who received 30 mg/day paroxetine from days 7 to 47, having previously received 10mg and 20mg/day. Medical history included a myocardial infarction 4 years previously. Isosorbide dinitrate (15mg daily) and metoprolol tartrate (300mg daily) were taken as concomitant medication throughout the study. There was a family history of mental illness. Her mother was suffering from mental disease when she died at 65 years, her father died at 62 years by committing suicide, and two brothers and two sisters have present recurrent depression.

The patient overdosed (on flunitrazepam) on day 40. She committed suicide by drowning on day 47 of the study period during treatment with active medication. Relationship to study treatment was given as "unknown". 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.

Patient 650.307.06282

Study Medication: Paroxetine

Cause of Death: Suicide (Shooting)

Case reference number 2000009299-1 is a clinical trial report from the single blind phase of blinded study 29060/650 for the treatment of post traumatic stress disorder. This report refers to a 35 year old male (patient identification number (650.307.06282).

The patient's medical history included a suicide attempt in 1993.

The patient received oral single blind paroxetine from 24 March 2000 until 30 March 2000 at dose 20mg daily. On 30 March 2000, 7 days after the first dose of study medication, the patient committed suicide with a gun in his car after his wife told him that she wanted a divorce.

The investigator considered this to be a serious event because it was fatal. An autopsy was not performed.

The investigator reported the suicide with a fire weapon as unrelated to treatment with study medication and to be probably associated with the family condition.

Patient 7124.012

Study Medication: Paroxetine

Cause of Death: Suicide (overdose)

This 42 year old female had been depressed for 16 weeks. She had experienced two other episodes of depression in the previous 10 years and had been treated with mianserin and maprotiline; neither gave a satisfactory response. For the current episode of depression she had received alprazolam 1.5mg daily for 3 weeks, clomipramine 300mg daily and thioridazine 150mg daily for one week, and she had been taking diazepam 15mg daily for 12 months. She also took oxazepam (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 overdosing with doxepin. The relationship of this event to paroxetine therapy was unknown.

Patient 057.012.1217

Study Medication: Placebo

Cause of Death: Suicide

This 32 year old male attempted suicide by taking 60 x 10mg temazepam capsules on day 29. Later in the study he ate toxic plants as a suicidal gesture (Day 57); he suffered from abdominal pain, nausea and headache (no doubt as a result of this). On Days 106 and 113, more than 14 days after the last dose of study medication, the patient made further attempts (toxic seeds and intoxication by motor car gas). Finally, 33 days after completion of the study, he died. His death was considered to be unrelated to trial therapy.

Patient 627.605.01012

Study Medication: Placebo

Cause of Death: Suicide

Case reference number 1999005430-1, is a clinical trial report from blinded study 29060/627 for post-traumatic stress disorder. This report refers to a 39 year old male (patient identification number 627.605.01012).

The patient's medical history includes major depression, social phobia, panic disorder, agoraphobia, obsessive compulsive disorder and suicidal ideation (since 1996). Concomitant medications include gliclazide, metformin hydrochloride and captopril.

The patient received oral study medication (placebo dose level 1) from 13 February 1999. On 19 February 1999, some 7 days after the first dose, the patient experienced severe depressive symptoms which worsened over the next 2-3 weeks. During this time, the patient experienced extreme post-traumatic stress disorder symptoms, including strong feelings of agitation, social withdrawal and suicidal ideation. (The patient was advised at last visit to seek extensive help, primarily electroconvulsive therapy). The patient was diagnosed as having acute depression. The patient was treated for the event with clotiapine, oxazepam and fluoxetine.

Treatment with study medication was stopped due to the depression on 01 March 1999 and the patient was withdrawn from the study. The patient reported to be feeling better and denied having any thoughts of suicide, however, at times, he appeared to be agitated. He was discharged from hospital on 12 March 1999. On 15 March 1999, the patient underwent electroconvulsive therapy as an out-patient (last treatment of 6) and his condition was reported as much improved. A follow-up visit was scheduled for 19 March 1999. The investigator considered this to be a serious event because it was life threatening, disabling, incapacitating and required hospitalisation.

The investigator reported the acute depression to be unrelated to treatment with study medication. The investigator reported that the event could be associated with the patient's primary condition.

On 18 March 1999, some 17 days after the last dose of study medication, the patient committed suicide by shooting himself. An autopsy was performed by the State Pathologist, but the report was unavailable.

The investigator reported the patient's suicide as unrelated to treatment with study medication. The investigator reported the event could be associated with the patient's primary condition and major depression.

Patient 785.721.00716

Study Medication: Placebo

Cause of Death: Suicide

This report refers to a 31 year old male (patient identification number 785.721.00716) who participated in double-blind study 29060/785 for the treatment of major depressive disorder with anxiety.

The patient's medical history included a hemangioma left facial distribution, allergy to pollen, and hayfever. The patient had no concomitant medication use.

The patient received study medication from 31 May 2001 to 10 Jul 2001. On 29 Jul 2001, 19 days after completing the study and the last dose of study medication, the patient's brother called to report the patient passed away. A second call from the patient's brother confirmed the patient committed suicide.

The investigator reported the suicide as not related to treatment with study medication and probably associated with major depressive disorder.

Patient 197.045.0322

Study Medication: Imipramine

Cause of Death: Suicide

On entry to the study (a comparison of paroxetine and imipramine in the treatment of depression and behavioural disturbance associated with dementia), this 70 year old Caucasian male had a history of headache and neck rigidity. He was stable on oxazepam on entry to the study. The present episode of depression had lasted for more than 1 year and had been treated with bi/tri/tetracyclic antidepressants and oral neuroleptics. He received imipramine in the study.

On day 13 the patient experienced severe restlessness lasting one day but recovered without sequelae. On day 22 the patient committed suicide (severe adverse experience of emotional lability) and was considered to have been withdrawn from the study. The investigator considered both events to be unrelated to study medication.

Patient 2371 054

Study Medication: Clomipramine

Cause of Death: Suicide (by hanging)

The patient was a 66 year old male with depression for 3 months. There had been one previous episode. Long term usage of nitrazepam, one tablet daily, was stopped on day 8. He had mild psychomotor retardation for the first 5 weeks of the study.

His baseline total bilirubin was 3.0 $\mu\text{mol/l}$ and the recorded value on day 42 was 55.4 $\mu\text{mol/l}$. SGPT and SGOT remained normal whilst alkaline phosphatase levels were just below the usual range of normal. In the absence of other comments, the raised bilirubin was regarded as being within the normal range. It is possible that there was, at some point, a transcription error from 5.54 $\mu\text{mol/l}$.

The patient had received clomipramine in the study. One month after the trial, the patient committed suicide by hanging. The patient took fluvoxamine during this last month.

Patient 6 67 002

Study Medication: Amitriptyline

Cause of Death: Suicide

This patient was a 36 year old male who received 150mg/day amitriptyline for 42 days as study treatment in study HP/83/67. Dry mouth, described as severe, was reported as an adverse experience. It had started 7 days before study medication was started and was still present at the end of the study. Mild sexual dysfunction and akathisia were reported, starting 2 and 12 days, respectively, after study medication was initiated. Both events had disappeared before the patient's final assessment.

The patient committed suicide on day 43, 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, with Hamilton and Montgomery and Asberg Depression rating scales indicating a reduction in depressive symptomatology, and, as is often the case, this may have given the patient the volition to kill himself.

Patient 7124 023

Study Medication: Imipramine

Cause of Death: Suicide (by shooting)

This 58 year old male had a 12 week history of depression which had been treated with doxepin 150mg daily for 5 weeks and maprotiline 150mg for 4 weeks. He received oxazepam 50mg daily from day -2 and this was continued throughout the study.

He started acebutolol 200mg daily from day 11 and ketoprofen 150mg daily from day14.

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

The patient experienced moderate impairment of urination and mild to moderate dry mouth, probably related to imipramine, moderate to mild 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.

Patient 7124 060

Study Medication: Imipramine

Cause of Death: Suicide (by hanging)

The patient was a 56 year old female who had had approximately 10 previous episodes of depression since her first episode in 1966. Duration of her episode on entry into the study was approximately 2 months. The patient received imipramine (150mg daily) from 01 Dec 1987, and was taking oxazepam (45 mg/day) concomitantly.

The patient committed suicide by hanging on 27 Dec 1987. She had made a previous suicide attempt about 9 months earlier in spring 1987. The investigator did not consider the death to be associated with exposure to study medication.
