[redacted]

5C

Document 5

27 August 1993

[redacted]
Director of Psychiatry
Prince Charles Hospital
Rode Road
CHERMSIDE QLD 4032

Dear [redacted]

Re: Paroxetine/Fluoxetine Clinical Trial (#356) – Suicide Attempts

As we have now received reports of 7 suicide attempts (including 2 deaths) for the (356) study comparing paroxetine and fluoxetine I am writing to all Investigators to provide you with further information and to reinforce SmithKline Beecham's viewpoint that they are unlikely to be causally related to paroxetine (or indeed fluoxetine). I understand that details of the cases have already been presented to you in the Study Newsletter which [redacted] distributes, however you may wish to submit the attached information to your IEC as well. We would, however, request a copy of your letter and their response for our files.

Attachment I lists the seven patients giving details of the duration of study drug administration and causal relationship to the study drug. In none of these cases was the code broken, therefore we do not know the percentage of patients receiving paroxetine or fluoxetine. Please also note that in all but one case causality was rated as "not" or "probably not" related to study drug and that there were other associated factors. In the last case, noted as "possibly related", the patient only received 1 dose of study drug. Moreover most of these cases were in-patients and represented more complicated management problems.

Suicide attempts or suicide in a clinical trial are of obvious concern to the Sponsor, Investigators and IEC, particularly when a new drug or drug class is involved. In 1991, SmithKline Beecham reviewed the prevalence and emergence of suicidal tendencies in patients treated with paroxetine in their clinical trials. This worldwide database of 4507 patients (2852 treated with paroxetine) was studied with respect to suicidal thoughts and behaviour during the treatment of depression. The findings of this review are summarised in Attachment II.

[redacted]

As stated SB is confident, based on the findings in this review, that treatment with paroxetine is not associated with increased risk of suicide ideation or behaviour. As such the number of suicide attempts in this study is within that expected as a consequence of the depressive illness *per se*.

We suggest, however, that all patients be monitored very closely for suicide ideation and general suitability for inclusion into this study. Please feel free to contact me if you or your IEC require further information or clarification.

Yours sincerely,

SmithKline Beecham Pharmaceuticals

[redacted]

ATTACHMENT I

PAROXETINE 356
SUICIDES & SUICIDE GESTURES

[redacted]

3. Patient: [redacted] Initials: [redacted]
Study Medication 19 Jun 1993 – [redacted]
Committed suicide s47F [redacted]

s22(1) [redacted]

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5. Patient: [redacted] Initials: [redacted]
Study Medication 27 Jul 1993 – [redacted]
Patient [redacted] was found dead s47F [redacted]

[redacted]

s22(1)

[redacted]

ATTACHMENT II

Summary of Position Paper

Lack of Suicidal Thoughts and Acts with Paroxetine (11/91)

[redacted] **Director CNS Therapeutic Unit, SB.**

Suicidal ideation is a universally recognised accompaniment to the symptomatalogy of depression and when acted upon by the patient, is the ultimate expression of the illness. Suicide accounts for approximately 15% of deaths in patients with mood disorder.[1]

Since the advent of effective antidepressant pharmacotherapy in the 1950's, clinicians have realised there is an increased risk of suicide early in treatment.[2] Depressed patients may exhibit some psychomotor retardation associated with suicidal ideation, and initial antidepressant therapy may help resolve motor retardation before alleviating suicidal thoughts. Freed from their retardation, patients may then actualise their suicidal impulses.[3]

In 1988, clinicians reported the worsening of depression and "development of suicidal ideation that was not present before treatment" in four patients all initially treated with desipramine. The worsening of depression and emergence of suicidal thoughts and behaviour were unrelated to typical tricyclic antidepressant adverse events and were not accompanied by signs of central nervous system toxicity. Exacerbation of depression and suicidal thoughts and behaviour resolved upon discontinuation of desipramine.

A similar emergence of suicidal thoughts has been reported for 6 patients receiving fluoxetine[5] these patients all had long and complicated psychiatric histories, their current depression being chronic and refractory. A causal relationship between fluoxetine and suicide/suicidal thought has not been revealed following a detailed analysis of the fluoxetine database.

To explore the effect of paroxetine on suicidal thoughts and behaviour during the treatment of depression, a review of the paroxetine worldwide clinical trial database, which forms the basis of paroxetine general marketing applications, has been conducted by SmithKline Beecham.

From this analysis a number of conclusions can be drawn.

- When paroxetine was given to patients with suicidal thoughts, these thoughts improved with continued therapy. This effect was seen with both paroxetine and active control, but to a greater extent with the former, when assessed using the more sensitive Montgomery Asberg Depression Rating Scale (MADRS).

- The dissociation which occurred between improvement in psychomotor retardation and suicidality, during treatment with paroxetine, was no different to that seen with either active control or placebo.

- In patients with no or only mild suicidal thoughts at the start of therapy, paroxetine did not cause a worsening of these features to any greater degree than placebo or active control.

- For patients with no suicidal thoughts at baseline, paroxetine, like active control, tended to 'protect' against the emergence of any suicidality. Assessment using the MADRS suggests this effect may actually be enhanced by paroxetine compared with active control.

- The appearance of suicidal ideation in placebo-treated patients previously devoid of these features, strongly suggested this emergence was most likely a part of the depressive illness rather than a pharmacotherapy induced phenomenon.

- Results on the SCL-56, a patient-completed scale, were in agreement with the above observer findings. Suicidal thoughts resolved more readily on paroxetine compared with placebo or active control. Emergent thoughts of ending one's life were also reduced on paroxetine.

- The anger/hostility cluster of the SCL-56 indicated that paroxetine and active control help resolve outwardly directed agression more effectively than placebo, and again there were some advantages of paroxetine over active control.

- Suicidality was no more common as a reported adverse event for patients on paroxetine compared with placebo or active control.

- Suicide attempts (including overdoses) were no more common with paroxetine therapy than with placebo or active control.

- Suicide attempts tended to occur early in therapy especially during the first 2 weeks of treatment with paroxetine, active control or placebo.

- The consequence of overdose with paroxetine alone was generally benign. Consciousness was usually retained, management was conservative and a successful outcome the norm.

In conclusion, the possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly close supervision of high-risk patients should accompany initial drug therapy.

REFERENCES:

1. Guze SB, Robins E: Suicide and primary affective disorders. Br. J. Psychiatry, 1970; 117: 437-438

2. Kreitman N: Social and Clinical Aspects of Suicide and attempted suicide In: Forrest A. (ed.): Companion to Psychiatric Studies: Churchill Livingstone: 38-63, 1973.

3. Mayer-Gross W, Slater E, Roth M (eds.): Clinical Psychiatry. Saunders, 1969.

4. Damluji NF, Ferguson JM: Paradoxical worsening of depressive symptomatology caused by antidepressants. J. Clin. Psychopharmacology, 1988; 8: 347-349.

5. Teicher MH, Glod C, Cole JO: Emergence of intense suicidal preoccupation during fluoxetine treatment. Am. J. Psychiatry, 1990; 147 (2): 207-210.

MONITORING VISIT [redacted]
[redacted] – PAROXETINE 356
31 AUGUST 1993

SAE'S

- TG received the letter regarding suicides. [redacted]

[redacted]

[redacted]

[redacted] 31/8/93

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PAROXETINE 356 STUDY

NEWSLETTER

SEPTEMBER 1993

[redacted]

Page 9-11 inclusive redacted under section 22(1) of the FOI Act (irrelevant information)