REGULATORY SUPPORTING DOCUMENT

PAROXETINE - CLINICAL WORSENING AND SUICIDE RISK IN ADULTS

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Paroxetine Adult Suicidality Analysis: Major Depressive Disorder and Non-Major Depressive Disorder

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) have been effectively used in the treatment of depressive illness and anxiety disorders since the late 1980s. A possible link between the use of SSRIs and suicidal behaviour was first described as a case series in the published literature in 1990 by Teicher et al, who reported that fluoxetine, the first SSRI introduced to the U.S. market, can induce or exacerbate suicidal tendencies. However, subsequent meta-analyses conducted shortly thereafter did not provide evidence supporting this claim, nor did an expert panel convened by FDA in 1991 find any compelling evidence for such an association.

This issue, i.e., whether there is an increased risk of suicidality (suicidal thinking or behaviour) associated with SSRI treatment, has been revisited periodically by GlaxoSmithKline (GSK, or legacy company SmithKlineBeecham) with regard to its SSRI paroxetine (Paxil®, Seroxat®, Aropax®, Deroxat®). As was the case for the earlier analyses of fluoxetine and suicidality in adults, these prior investigations of paroxetine's potential association with treatment-emergent suicidality did not produce evidence suggestive of an association in adults. For example, an analysis conducted by GSK in 2002 examined the incidence of attempted suicide in all placebo-controlled paroxetine trials in patients with depression. The incidence of suicide attempts in the paroxetine group was 2.1% (66/3192) compared to 1.9% for placebo (38/2047). This difference was not statistically significant (p=0.61).

While lack of appropriate treatment is clearly the largest contributor to suicide risk in depressed patients, concerns about SSRI treatment and a possible link to suicidality in some patients have persisted since Teicher first raised this issue. These concerns were heightened further with the recent finding that treatment with SSRIs, including paroxetine, were associated with an increased risk of suicidality relative to placebo in paediatric patients enrolled in controlled clinical trials. Partly as a result of this finding in paediatric patients, a number of regulatory agencies (including the FDA, and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK) have revisited this issue in adults, particularly in young adults. In May of 2003, an Expert Working Group (EWG) of the Committee on Safety of Medicines was convened in the UK to investigate ongoing public safety concerns with SSRIs, in particular around suicidal behaviour and withdrawal reactions/dependence. As part of this review, SSRI manufacturers (including GSK) provided clinical trial data to the EWG in order for this group to conduct its own assessment. The EWG also evaluated available epidemiologic data from the UK General Practice Research Database (GPRD), as well as data from other sources including published literature and spontaneous reports from healthcare professionals.

Upon completion of its analyses, with respect to SSRIs as a class the EWG concluded:

- from the available adult clinical trial data, a modest increase in the risk of suicidal thoughts and self-harm in those taking SSRIs compared with placebo could not be ruled out;
- there was no clear evidence of an increased risk of self-harm and suicidal thoughts in young adults; however, given that individuals mature at different rates and that young adults are at a higher background risk of suicidal behavior than older adults, as a precautionary measure young adults treated with SSRIs should be closely monitored;
- there was insufficient evidence from clinical trial data to conclude any marked difference between members of the SSRI class, or between SSRIs and active comparators, with respect to their influence on suicidal behaviour; and,
- evidence from non-experimental GPRD studies indicated that in adults there was no increased risk of suicidal behaviour with SSRIs compared with TCAs.

As part of its review, the EWG also conducted a meta-analysis of the adult clinical trials of paroxetine and concluded:

- there was no strong evidence of an increased risk of suicidal events for adult patients with depression exposed to paroxetine compared to placebo, although the point estimates and confidence intervals were consistent with a possible increase in risk.

During the same time period, the MHRA referred paroxetine to European (EU) regulatory authorities for an EU-level review (known as the "Article 31 Referral"). As part of this process, GSK was asked to provide specific analyses of its clinical trial data to evaluate the risk of suicide, suicidal thoughts and self-harm, with particular attention to potential risk factors including age and gender. GSK submitted the 1st set of analyses to the initial Article 31 questions in September 2003 and submitted the 2nd set of analyses in January 2004. Overall, i.e., in all indications studied in placebo-controlled trials in adults, the incidence of possible suicide-related events (i.e., thoughts and behaviours) was similar in the paroxetine and placebo groups (0.8% vs. 0.9%, respectively; OR 0.8 [95% CI 0.6, 1.2]). The findings were similar in the studies conducted specifically in patients with depression (1.7 vs. 1.9%, respectively; OR 0.9 [95% CI 0.6, 1.3]). In the 18-29 years age group, for all indications, the incidence of possibly suicide-related events was greater in the paroxetine group (1.8%) than in the placebo group (1.4%), although this difference was not statistically significant (OR 1.3 [95% CI 0.7, 2.3; p=0.46]).

In April 2004, the EU scientific committee (CHMP) reached their conclusions with respect to paroxetine use in adults, which are summarized as follows:

- The benefit/risk balance for paroxetine remains favourable across all adult indications; and
- There is a possibility of an increased risk of suicidal behaviour associated with paroxetine in young adults (18-29 years), although the increased risk was not statistically significant. In the older age groups no such increase was observed. Results from observational studies indicate no increased risk of suicidality in patients who were prescribed paroxetine and likewise, post-marketing reports indicate low rates of suicidal related behaviours. Clinical trials show similar low rates in placebo and paroxetine treated

depressed patients. Rates in patients with other disorders for which paroxetine is indicated are similarly low.

In December 2004 the CHMP reaffirmed these conclusions following consideration of three new epidemiology studies which utilized the UK General Practice Research Database. That same month (Dec 2004) FDA initiated steps to enable its own examination of the relationship between antidepressant use and suicidality in adult patients by requesting all antidepressant manufacturers to provide specified patient-level data from all acute (i.e., ≤ 17 week), double-blind, randomized, placebo-controlled adult studies in major depressive disorder. Potential cases of suicidality were identified via adverse event text string searches, review of serious adverse event (SAE) narratives (including all deaths), and review of the comment fields from the Case Report Forms (CRFs) for all relevant studies. As part of this process, GSK contracted with Columbia University to have independent experts selected by Columbia blindly review each potential case of suicidality and classify the events into suicidal or non-suicidal categories using the same approach used in the paediatric suicidality review conducted by FDA.[†] In May of 2005, FDA expanded its request to also include all acute non-MDD studies (e.g., studies in anxiety disorders such as OCD, Panic Disorder, Social Anxiety Disorder, etc.). At this time GSK has fully complied with these requests from FDA, i.e., GSK has submitted all required data to FDA (the only exception being the data from one small study conducted in the UK for which the data were not readily available and are currently being retrieved [study #298]).

Recently, GSK decided to conduct its own analyses of the datasets provided to FDA. A briefing document with the results from MDD datasets was submitted to the Dutch Medicines Evaluation Board (MEB) on 9th March 2006 and subsequently to all EU Concerned Member States. GSK now has completed its analyses of both the MDD-specific and non-MDD specific datasets. This latter group includes the following clinical populations: dysthymic disorder, intermittent brief depression (IBD), bipolar depression, panic disorder, obsessive compulsive disorder (OCD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), alcohol dependent patients (undergoing detoxification), and fibromyalgia. Before conducting this analysis, GSK consulted with external experts to obtain their advice and thoughts as to how to undertake this analysis. In addition, GSK's final statistical analysis plan was submitted on an informational basis to FDA in late December 2005, and to the Dutch MEB (Reference Member State in the EU) in early February 2006.

2. Brief Overview of Methods

The analysis plan developed by GSK for the present analysis of the adult suicidality data (see Appendix I) is based, in part, on methods used previously by FDA during their analysis of paediatric suicidality data. The analysis plan also reflects advice

[†] It should be noted that events were coded by Columbia University in accordance with numerical codes specified by FDA for this review of adult data. These codes differ slightly from those used for the previous FDA review of paediatric studies, owing to the fact that there were no completed suicides in any of the SSRI pediatric trials.

received by external consultants with expertise in suicidality. Because GSK previously conducted a similar analysis of suicidality data for paroxetine as part of the Article 31 Referral process in 2003, it is important to consider key methodologic differences between the previous and current analysis (see Table 1, below).

Table 1. Key Differences Between Previous Article 31 Analysis and Current Analysis

	Article 31 Analysis	Current Analysis
Events adjudicated by external experts (Columbia University)	No	Yes
Search algorithm for AEs	Algorithm-based search of AE fields	Algorithm-based search of AE fields plus review of CRF comment fields and SAE narratives
Statistical methods	Pooled analysis (crude odds ratios)	Exact method, adjusted by trial (primary method)
Definition of young adults	18-29 yrs	18-24 yrs
Included trials of any duration (ie, included long-term trials where available)	Yes	Yes
Depression analysis – trial groupings	Depressive illnesses together	By indication (eg, MDD, Intermittent Brief Depression, Dysthymia, etc.)
Depression analysis – number of trials	26 depression trials (Dec 1982 through Aug 2001)	19 MDD trials (Dec 1982 to date; ie, through May 2005)
All indications analysis – number of trials	171 studies, including 50 placebo-controlled parallel group trials	57 trials, all placebo-controlled parallel group trials

2.1 Comparison of statistical methods

The analysis of suicidality data has been conducted using two statistical methods for estimating the common odds ratio and its confidence interval, as well as testing the null hypothesis that the common odds ratio is equal to 1. The primary analysis used an exact approach (Mehta et al, 1985) implemented in the statistical software StatXact®. The second approach was to use the Mantel-Haenszel (MH) method, with 0.5 continuity correction (Sutton et al, 2002) applied at the level of the trial. GSK used this additional approach because it was the same one used by FDA in its analysis of the paediatric datasets.

In some cases the results of the analysis of the MDD trials from the two methods diverge substantially. Notably, the odds ratios for Definitive Suicidal Behaviour for the MDD population are 6.7 (by the exact method) and 1.6 (by the MH method). The

lower odds ratio estimated by the MH method is explained by the addition (under the continuity correction) of 4.5 events to each of the treatment groups which, proportionately, yields a greater increase in the placebo group than in the paroxetine group.

For the endpoint of Rating Scale Emergent Behaviour in the MDD population, there is one event on paroxetine (0.03%) and zero events on placebo (0%), but the MH method estimates the odds ratio to be 0.4 (indicating *lower* risk with paroxetine than placebo). This is a result of the imbalanced randomization in study 009, in which the one event occurred.

With this MDD dataset, **GSK believes the MH method with continuity correction substantially underestimates the odds ratio for Definitive Suicidal Behaviour compared with the exact method, because of the small and disproportionate number of events observed between the two treatment groups and because of the imbalanced randomization in some of the trials**. The exact method is not affected by either of these problems, and is designed particularly for sparse datasets such as this. We believe the exact method is the most appropriate statistical method for the assessment of this dataset, and should be used in preference to the MH method with continuity correction.

3. Clinical Summary

3.1. Major Depressive Disorder

GSK has completed its analysis of paroxetine placebo-controlled clinical trials in patients with Major Depressive Disorder (MDD); see Appendices II - IV. A brief summary of key findings follows:

- On the primary endpoint of **definitive suicidal behavior or ideation**, there was no statistically significant difference between adults with MDD treated with paroxetine compared to placebo (31/3455 (0.90%) vs. 11/1978 (0.56%); odds ratio = 1.3 (95% CI 0.7, 2.8); p=0.493).

- The results provide evidence of an increase in **suicide attempts** in adults with MDD treated with paroxetine compared to placebo; however, as the absolute number and incidence of events are very small (11/3455 (0.32%) for paroxetine, vs. 1/1978 (0.05%) for placebo; odds ratio = 6.7 (95% CI 1.1, 149.4); p=0.058), these data should be interpreted with caution.

- There were proportionally slightly more events (suicidal behavior with or without ideation) in **young adults** between 18-24 years of age with MDD treated with paroxetine (5/230 (2.17%)) compared to placebo (0/104 (0%)) than in older adults, however these data are not conclusive due to the relatively small sample size of the 18-24 age group and the small number of events. These trends are consistent with findings from previous analyses in pediatrics and adolescents, and while it appears that the risk seen in pediatrics seems to extend beyond age 18, the extent to which this occurs is less clear.

- Although GSK's pre-defined analysis plan did not examine risk in adults aged 25-30 years, it should be noted that review of the 11 cases of definitive suicidal behavior has indicated that five of these patients were aged 25-30 years. Hence, a total of eight of the 11 paroxetine-treated MDD patients with suicidal behavior were aged 18-30 years. This observation suggests that the increased risk of suicidal behavior seen with the overall MDD population was driven primarily by events occurring in the younger adult population.

- 10 of the 11 paroxetine-treated patients with suicidal behavior had experienced improvement in their major depression; and most (9 of 11) of the paroxetine-treated patients had an identified social stressor at the time of the suicide attempt.

- The analysis provided substantial evidence for efficacy in the overall adult MDD population. Paroxetine-treated patients had a significantly greater reduction in HAMD or MADRS from baseline than did placebo. When defining treatment response as a 50% or greater reduction in the primary outcome measure (either the HAMD or MADRS total score), significantly more paroxetine subjects (52.3%) than placebo subjects (37.1%) responded during the clinical trial.

- There was also evidence of efficacy for young adults aged 18-24, although the results indicated some variability in response depending on the depression scale used (ie, HAM-D vs. MADRS). These data are limited, however, due to the small sample size of the 18-24 age group.

- The overall risk-benefit of paroxetine in the treatment of adult patients with MDD remains positive.

The finding of evidence of increased suicide attempts in adults with MDD treated with paroxetine compared to placebo is new, and was not found in GSK's Article 31 analysis or in GSK's prior analyses of suicide attempts. In the Article 31 analysis of self-harm in patients with depressive illness, there were 45 events reported in 3421 patients treated with paroxetine (1.3%), and 33 events in 2117 patients treated with placebo (1.6%), for an odds ratio of 0.84 (95% CI 0.54, 1.32). In contrast, the current analysis of definitive suicidal behavior[†] in patients with MDD revealed 11 events in 3455 patients treated with paroxetine (0.32%), and 1 event in 1978 patients treated with placebo (0.05%); odds ratio 6.7 (95% CI 1.1, 149.4). There are two likely explanations for the difference in results between the prior Article 31 analysis and the current analysis: the datasets included in the analyses, and the methodology used for identifying the relevant events. With respect to the datasets, the current analysis was restricted to a single indication, MDD, consistent with FDA's approach. In terms of the methodology used to identify events, the cases comprising the current analysis were individually reviewed by external experts who were blinded to treatment. As a consequence of the above two factors, 36 events in the paroxetine group and 33 events from the placebo group that were included in the Article 31 analysis of

[†] "Definitive suicidal behaviour" included events classified as completed suicide, suicide attempt, and preparatory acts toward imminent suicidal behaviour. In the results of the current analysis, there were no completed suicides nor events classified as preparatory acts (ie, all events were classified as suicide attempt).

self-harm were not included in the present analysis. The majority of these events (33 paroxetine and 33 placebo) were from two trials investigating intermittent brief depression, and involved patients with a previous history of suicidality. The remaining 3 paroxetine cases were not classified as suicidal behavior by the expert raters. Additionally, there were an additional 2 events identified in the paroxetine group and 1 event in the placebo group that were not identified by the methods used in the Article 31 analysis.

3.2. Non-Major Depressive Disorder

GSK has recently completed its analysis of paroxetine placebo-controlled clinical trials in patients with non-Major Depressive Disorder (non-MDD); see Appendices V - VII. A brief summary of key findings follows:

- In placebo-controlled clinical trials in psychiatric disorders other than MDD, there was no evidence of an increased risk of **suicidal behaviour or ideation** (primary endpoint) in patients treated with paroxetine.
    - "All Indications": 0.93% vs 1.09%; OR 0.9 [95% CI 0.7, 1.3]; p=0.649
    - "All Depression": 1.77% vs 2.08%; OR 1.1 [95% CI 0.7, 1.7]; p=0.671
    - "All Non-Depression": 0.32% vs 0.49%; OR 0.7 [95% CI 0.3, 1.3]; p=0.293

  (Numbers for "All Indications" and "All Depression" include the data from MDD trials).

- There was no evidence of treatment difference in **suicidal behavior** alone (secondary endpoint) in any overall population grouping:
    - "All Indications": 0.56% vs 0.67%; OR 1.2 [95% CI 0.8, 1.9]; p=0.483
    - "All Depression": 1.16% vs 1.59%; OR 1.2 [95% CI 0.7, 1.9]; p=0.613
    - "All Non-Depression": 0.13% vs 0.11%; OR 1.5 [95% CI 0.4, 5.8]; p=0.759

- Although not statistically significant, there were proportionally slightly more events (suicidal behavior with or without ideation) in **young adults** between 18-24 years of age with psychiatric disorders other than MDD treated with paroxetine (0.99% for paroxetine versus 0.25% for placebo). This finding was consistent across the non-MDD indications.

- Suicidal behaviour alone was slightly higher in young adults treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant.

- There was evidence of substantial efficacy in the non-MDD population. When defining response as a Clinical Global Impression (CGI) score of "much improved" or "very much improved," significantly more paroxetine subjects (58.8%) responded compared to placebo subjects (39.9%) in the non-depression population.

- As measured by CGI, there were significantly more responders in the paroxetine group versus the placebo group for: panic disorder (68.3% v. 47.4%); OCD (38.3% v. 23.3%); SAD (53.9% v. 31.1%); GAD (64.5% v. 49.4%); PTSD (58.2% v. 39.6%); and PMDD (68.9% v. 42.3%). For each of these populations, there was significant improvement in disease-specific rating scales for paroxetine-treated patients compared to placebo-treated patients.

- Efficacy in young adults was comparable to that in older adults in the non-MDD population.

4. Summary of the Findings and Conclusions

Based on the findings from the MDD and non-MDD datasets, GSK believes that young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine. An analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo, although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed.

In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

The analysis revealed substantial evidence of efficacy in all indications. Efficacy of younger adults was comparable to efficacy in older adults.

It is difficult to conclude a causal relationship between paroxetine and suicidality due to the small incidence and absolute number of events, the retrospective nature of this meta-analysis, and potential for confounding by the fact that the events of interest are a symptom of the psychiatric illnesses themselves. Although these most recent findings reveal evidence of a possible increased risk for suicidal behaviour in adult patients with MDD and for younger adults for suicidal behaviour or ideation with MDD and non-MDD disorders, we believe that the overall risk-benefit assessment for the young adult and the adult patient population remains positive.

5. Changes to GSK Core Safety Information

Based on these most recent findings in the adult patient dataset, GSK has concluded that changes to the Core Safety Information for paroxetine are warranted. The revised information relating to clinical worsening and suicide risk in adults is as follows:

Clinical worsening and suicide risk in adults

Young adults, especially those with MDD, may be at increased risk for suicidal behaviour during treatment with paroxetine. An analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]; all of the events were suicide attempts). However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. This risk persists until significant remission occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery. Other psychiatric conditions for which paroxetine is prescribed can be associated with an increased risk of suicidal behaviour, and these conditions may also be co-morbid with MDD. Additionally, patients with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts. All patients should be monitored for clinical worsening (including development of new symptoms) and suicidality throughout treatment, and especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases.

Patients, (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognised that the onset of some symptoms, such as agitation, akathisia or mania, could be related either to the underlying disease state or the drug therapy (*see Akathisia and Mania and Bipolar Disorder below; Adverse Reactions*).

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

References

Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990, 147(2):207-10.

Mehta CR, Patel NR, and Gray R. Computing an exact confidence interval for the common odds ratio in several 2x2 contingency tables. *Journal of the American Statistical Association* 1985, Vol 80, no 392.

Sutton AJ, Abrams KR, Jones DR, Sheldon TA, and Song F. Methods for meta-analysis in medical research. *John Wiley & Sons*, NY 2002 page 69.

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