

**Jackie
Westaway-1**

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To: Barry Brand, Bonnie Rossello, Lionel D Houle, Jackie C Owens, Pascale Richetta, Beatrix Steffen, Luis DE LORENZO, Ken DiPangrazio, Roland Kaan, Eddy R Beke, Frank D Auton, B Srinivasan, Christophe Weber

cc: Julie Wilson-1, Sarah Daniels-1, Jill Andrews-1, Margaret M Black, Keiron T Sparrowhawk, Graham Griffiths-1, Susanne Borrett-1, Fiona Barnard-1, Paul Jenner-1, Jane M Nicholass, Anne J Bell

Subject: Seroxat/Paxil in Adolescent Depression

Please find attached to this memo a position piece, prepared by Julie Wilson of CMAT, summarising the results of the clinical studies in Adolescent Depression.

As you will know, the results of the studies were disappointing in that we did not reach statistical significance on the primary end points and thus the data do not support a label claim for the treatment of Adolescent Depression. The possibility of obtaining a safety statement from this data was considered but rejected. The best which could have been achieved was a statement that, although safety data was reassuring, efficacy had not been demonstrated. Consultation of the Marketing Teams via Regulatory confirmed that this would be unacceptable commercially and the decision to take no regulatory action was recently endorsed by the TAT.

As you will see from the position piece the positive trends in efficacy which were seen in Study 329 are being published as a poster at ECNP this year and a full manuscript is in development. Published references will therefore be available for the study. There are no plans to publish data from Study 377.

This report has been prepared for internal use only, Data on File summaries will be prepared and issued once the final reports from the studies have been approved. This position piece will also be available on The Seroxat/Paxil resource database

Best wishes

Jackie Westaway

SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies
FOR INTERNAL USE ONLY

SITUATION

2 SB sponsored, placebo-controlled, phase III clinical trials have been conducted, Study 329 (US) and Study 377 (Europe, South America, South Africa and Saudi Arabia), in order to assess the efficacy and safety of Seroxat/Paxil (up to 40mg/day) in the treatment of adolescents (aged between 13 and 18 years and 11 months) with unipolar major depressive disorder (diagnosed according to DSM IIIR, Study 329 or DSM IV criteria, Study 377).

Study 329 was a placebo-controlled, imipramine comparator study with an 8 week acute treatment phase followed by a 6 month extension phase. The acute phase has completed and the extension phase is due to complete at the end of 1998. 275 patients were recruited to the study. Results from the acute phase of this study show that there were no statistically significant differences from placebo on either of the primary efficacy parameters (change from baseline in HAMD total scores and the proportion of responders-where response was defined as a $\geq 50\%$ reduction from baseline in HAMD score or a HAMD score ≤ 8 at endpoint). However, trends in favour of paroxetine compared with placebo were seen across all the indices of depression (change from baseline in HAMD total [p=0.133], HAMD responders [p=0.112], CGI [p=0.094] and K-SADS [p=0.065] scores) and statistically significant differences from placebo were observed in the proportion of patients in remission (defined as a HAMD score of ≤ 8 at endpoint). In general, the response to imipramine was similar to that for placebo. The 6 month extension phase is ongoing and is scheduled to complete at the end of 1998.

Study 377 was a 12 week placebo-controlled study, conducted in 276 adolescents with major depression. There was a high placebo response rate in this study and no statistically or clinically significant differences from placebo were observed on either of the primary efficacy variables (proportion of patients achieving a $\geq 50\%$ reduction from baseline in total MADRS scores and change from baseline in the K-SADS-L depressive subscale score). The only differences from placebo (secondary efficacy variables) were seen in a subgroup of patients who were ≥ 16 years of age.

Possible explanations for the high placebo response include;

- 1) The large number of study visits
- 2) the duration of the assessments
- 3) The fact that concomitant psychotherapy was not excluded
- 4) Question marks about the adequacy of using currently available diagnostic criteria and rating scales in younger patients
- 5) Adolescents may be more susceptible to a placebo effect
- 6) Developmental issues. Children and adolescents may respond in a pharmacologically different manner due to quantitative and/or qualitative differences in neurotransmitter/receptor systems.

Conclusions from these studies:

- There were no differences in the safety profile of Seroxat/Paxil in adolescents when compared to that already established in the adult population
- The efficacy data from the above clinical trials are insufficiently robust to support a regulatory submission and label change for this patient population.

OTHER DATA:

Ongoing studies: SB France are conducting a locally funded double-blind, comparative study of Seroxat/Paxil with clomipramine in adolescents with major depression (Study 511). In addition, a study in adolescents with OCD (Study 453) is underway in the US. This study comprises a 16 week open label Seroxat/Paxil treatment phase, followed by double-blind, randomisation to paroxetine or placebo for a further 16 weeks of treatment. The regulatory acceptability of these 2 studies needs to be established.

Published data: A review of the literature shows that 2 studies assessing the use of paroxetine in the treatment of 34 adolescents and children with depression have been published (Rey-Sanchez F and Gutierrez-Cesares, 1997; Findling et al; 1996).

COMPETITOR ACTIVITIES:

Lilly are believed to be in near to completing their phase III clinical trials in adolescent depression. One relatively large placebo-controlled 8 week study with an open 12

month follow-up period conducted in 96 patients (aged 8-18 years) has recently been published (Emslie et al; 1997 and 1998). These data show that 56% (27/48) patients on fluoxetine (20mg/day) compared with 33% (16/48) patients on placebo were rated as much or very much improved on the CGI at Week 6 ($p=0.02$). In the 12 month follow-up period, 85% ($n=74$) patients recovered from the depressive episode (47 on fluoxetine, 22 on placebo and 5 on other antidepressants or lithium). Twenty nine (39%) of the patients (36% of those who had recovered on fluoxetine [17/47] and 41% of those who had recovered on placebo [9/22] had a recurrence of depression during the 12 month follow-up (a higher recurrence rate than seen in adults). Other published data on fluoxetine are from small open studies or individual case reports (Colle et al; 1994).

Pfizer already have positive data (including PK data) and are licenced in the US for the treatment of adolescent OCD. In addition, Pfizer are also believed to be conducting clinical trials in adolescent depression. Available published data are limited, derived from small open studies in adolescent depression (McConville et al; 1996; Tierney et al; 1995)

TARGET

To effectively manage the dissemination of these data in order to minimise any potential negative commercial impact.

PROPOSALS

- Based on the current data, and following consultation with SB country regulatory and marketing groups, no regulatory submissions will be made for either efficacy or safety statements relating to adolescent depression. The rationale for not attempting to obtain a safety statement is as follows;
 - i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use
 - ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.
- Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.

- The regulatory acceptability of Studies 511 and 453 and any other data in this patient population will continue to be investigated.

REFERENCES

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7. Tierney E, Joshi PT, Llinas JF et al. Sertraline for major depression in children and adolescents: Preliminary clinical experience. *J Child Adolesc Psychopharmacol*; 1995; 5 (1):13-27.

Statement for the markets

Summary of the Seroxat/Paxil clinical trials in Adolescent Depression

Results from the 2 placebo-controlled, phase III clinical trials designed to assess the efficacy and safety of Seroxat/Paxil in adolescents with major depression are now available.

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures. The second study (study 377), which was conducted in Europe, South America, South Africa and Saudia Arabia, showed a high placebo response rate and failed demonstrate any separation of Seroxat/Paxil from placebo.

Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities. Results from Study 329 will be presented in abstract form at the ECNP meeting (Paris, November 1999) and a full manuscript will be progressed. There are no plans to publish data from Study 377.