SmithKline Beecham
Pharmaceuticals

Marketing Department

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TO: SK&F Consultants
SBP Consultants
Psychiatric Consultants
Hospital Product Specialists
Managed Care Specialists
Federal Military Specialists
Janssen Consultants

cc: Jules Armson — AVPs
Walt Graham — RVPs
Steve Martinelli — DSMs
Kathryn O'Fee — RTRs
Howard Pien — RMAs
Bonnie Rossello

FROM: Barry Brand
Assistant Product Manager, *Paxil*

SUBJECT: METANALYSIS EXAMINING SUICIDAL IDEATION - APPROVED FOR USE

A metanalysis, recently published in the peer-reviewed journal European Psychopharmacology, examined whether *Paxil* was associated with any increase in suicidal thoughts or acts. *Paxil* showed a statistically significant advantage in reducing suicidal thoughts in all analyses compared with placebo. On the Montgomery Asberg Depression Rating Scale (MADRS) there was a significant advantage compared with active controls at weeks 1, 3, 4 and 6 ($P<0.01$). In the analysis of the data from controlled studies and open extension studies of *Paxil* calculated by patient year of exposure there were 2.8 fewer suicides in the *Paxil*-treated group compared with active control and 5.6 times fewer compared with placebo. Clearly, very positive results.

This paper has been approved for use with physicians to alleviate any concerns they may have regarding suicidal ideation. Suicide continues to be an important public health issue, ranking eighth among all causes of death in the U.S. It is generally estimated that 15% of depressed patients take their own lives (see page 11, last paragraph). While *Prozac* has demonstrated no increase in suicidal ideation, reports in the lay press continue to make suicidal ideation an issue for *Prozac*, and by extension the SSRIs in general.

The metanalysis looked at pooled data from three data sets:

1. Pooled data from all *Paxil* world-wide, controlled, short-term (up to 6 weeks), efficacy studies. These were all double-blind parallel-group comparison studies in moderate to severe major depression. Data were available for 2852 patients treated with *Paxil*, 554 with placebo and 1101 with reference antidepressants. Analysis of suicidal thoughts on the HAMD was carried out on this total database of 4507 patients.

2. Pooled data from all studies conducted that used the MADRS and symptom check list (SCL-56). Data were available for 1510 patients treated with *Paxil*, 459 with an active control and 454 with placebo. Analysis of suicidal thoughts was made on the MADRS in this database of 2423 patients and on the SCL-56 in 2371 patients for whom the SCL-56 was available.

3. Pooled data from a six-center U.S. placebo controlled trial comparing *Paxil* and imipramine. These trials used an identical protocol and provide the most direct comparison and as such were reviewed separately. Data were available for 234 patients treated with *Paxil*, 233 with imipramine and 235 with placebo. Suicidal thoughts on the HAMD and MADRS were analyzed in this database of 702 patients.

The tables on the next page (taken from table 1, page 7) summarize data from the U.S. placebo-controlled six center trial. *Paxil* was significantly better than placebo on the MADRS at weeks 1, 2, 3, 4, and 6 whereas imipramine was superior to placebo only at week 6. It is also interesting to note that *Paxil* was significantly better than imipramine at week 1.

Plaintiff Exhibit
PX-100

MADRS Suicidal Thoughts Item - Mean Scores Over Time (0 = Enjoys Life / 6 = Explicit Plans of Suicide)						
	Week					
	Baseline	1	2	3	4	6
Paxil	1.75	1.20[1,2]	0.95[1]	0.82[1]	0.63[1]	0.48[1]
Placebo	1.77	1.42	1.20	1.14	0.97	0.92
Imipramine	1.84	1.47	1.11	0.97	0.77	0.45[1]

[1]Significant advantage compared with placebo ($p<0.01$)
[2]Significant advantage *Paxil* vs. imipramine ($p<0.01$)

HAMD Suicide Item - Mean Scores Over Time (0 = Absent / 4 = Suicide Attempt)						
	Week					
	Baseline	1	2	3	4	6
Paxil	0.96	0.63[1]	0.47[2]	0.37[2]	0.29[2]	0.20[2]
Placebo	1.01	0.77	0.65	0.59	0.54	0.45
Imipramine	1.00	0.70	0.50	0.42[1]	0.32[2]	0.16[2]

[1]Significant advantage compared with placebo ($p<0.05$)
[2]Significant advantage compared with placebo ($p<0.01$)

Table 2 on page 8 summarizes data from all controlled studies that used the MADRS (n=2423). Results are summarized as following:

> *"There was a significantly greater amelioration in score in the paroxetine group compared with placebo at all post-baseline assessments (weeks 1, 2, 3, 4, and 6) (P<0.01). There was a significant advantage for paroxetine compared with active reference control at weeks 1, 3, 4, and 6 (P<0.01). There was a significantly greater amelioration in score in the active reference control group compared with placebo only at weeks 1 and 2."* [page 8, column 2, paragraph 1]

Additional support is provided from the world-wide data set for which results are analyzed and summarized in table 3 on page 8. The paper goes on to look at emergent suicidal thoughts finding that *"...emergent scores were more frequent for placebo-treated patients compare with those receiving either paroxetine or imipramine."* [page 9, column 1, paragraph 2] With regard to actual suicides calculated per patient year of exposure, ***"... there were 2.8 times fewer suicides in the paroxetine-treated group compared with active control and 5.6 times fewer compared with placebo."*** [page 10, column 1, paragraph 3] Nine patients attempted suicide involving the overdose/ingestion of *Paxil* alone, the largest single dose being 850 mg -- all patients recovered uneventfully (see page 10, column 2, paragraph 2).

This paper adds to the burden of proof that *Paxil* is a safe and effective antidepressant and may be used with physicians to alleviate any concerns they may have regarding suicidal ideation. Although reprints are not currently available you may use this paper with physicians, but may not leave behind. A copy of this paper is included in this weeks field mail.