# EXHIBIT 7

**RE: USE OF WELLBUTRIN SR® FOR THE TREATMENT OF ANXIETY-RELATED DISORDERS**

## SUMMARY


- Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets are indicated for the treatment of depression in adults. Wellbutrin SR is not indicated for the treatment of anxiety disorders.

- Bupropion has demonstrated positive results in treating symptoms of anxiety in anxious depressed patients. Controlled clinical trials have demonstrated that the efficacy of bupropion in treating the symptoms of anxiety associated with depression is comparable to that of Zoloft® (sertraline HCl, Pfizer Inc), Prozac® (fluoxetine HCl, Dista Products), and Paxil® (paroxetine HCL, GlaxoSmithKline).

- Pooled data from two identical randomized comparative clinical trials demonstrated no differences between Wellbutrin SR or sertraline in achieving anxiolysis in anxious depressed patients or in resolution of depressive symptoms, regardless of the degree of baseline anxiety.

- Pooled data from two identical randomized comparative clinical trials demonstrated that baseline anxiety did not predict preferential response to either Wellbutrin SR or sertraline and should not be a basis for selecting between treatments.

- Bupropion has not been extensively evaluated for the treatment of anxiety disorders. Open-label clinical trials describe the successful use of bupropion in the treatment of post-traumatic stress disorder and social phobia. Limited clinical experience suggests that bupropion may be useful in the treatment of panic disorder, however controlled trials are needed.


**Some of the information contained in this letter may be outside the product labeling for GlaxoSmithKline products. This letter is not intended to offer an opinion on the advisability of administering any products in a manner inconsistent with product labeling. In order to allow GlaxoSmithKline to monitor the safety of Wellbutrin SR, we encourage clinicians to report suspected overdoses or adverse effects to our Product Surveillance Department (1-888-825-5249). Please consult the enclosed product information for full prescribing details.**

## BACKGROUND

Bupropion, a novel new-generation antidepressant with dual neurotransmitter properties, is a norepinephrine and dopamine reuptake inhibitor (NDRI) (1). Bupropion has no clinically significant effect on serotonin neurotransmission and essentially no affinity for muscarinic, histaminergic, dopaminergic, or alpha-adrenergic receptors.

Norepinephrine, dopamine, and serotonin are the neurotransmitter pathways believed to be important in the pathophysiology and treatment of depression. While they are equally important in the regulation of mood, research suggests that these neurotransmitter pathway systems differ in their effects on behavior and emotion. Norepinephrine and serotonin, in addition to their effects on mood, have both been shown to be important in regulating anxiety (2,3,4,5).

Bupropion demonstrated superior efficacy over placebo for the treatment of depression in two placebo-controlled trials (6,7) Further studies comparing bupropion to placebo and either sertraline (8,9) or fluoxetine (10,11,12) in depressed patients also showed efficacy similar to the active treatment. Active-controlled trials versus sertraline (13), fluoxetine (14), paroxetine (15), and several TCAs (16,17,18,19,20) also demonstrated comparable efficacy for the treatment of depression. The efficacy of bupropion in treating the symptoms of anxiety associated with depression was similar to the SSRIs and TCAs in these comparative trials.

## CLINICAL INFORMATION

### Wellbutrin SR versus sertraline

Pooled data from two identical, 8-week, double-blind, placebo-controlled trials of Wellbutrin SR 150-400 mg/day, sertraline 50-200 mg/day, and placebo in depressed patients demonstrated that treatment with Wellbutrin SR and sertraline resulted in a greater than 50% improvement in Hamilton Rating Scale for Anxiety (HAM-A) scores with no between-group differences observed on any treatment day (Figure 1) (21). A lack of relationship between baseline anxiety and antidepressant response or remission status was consistent across all treatment groups (Figure 2) (22).

**Figure 1: Mean HAM-A Scores in Depressed Patients Treated with Wellbutrin SR, Sertraline, or Placebo (21)**

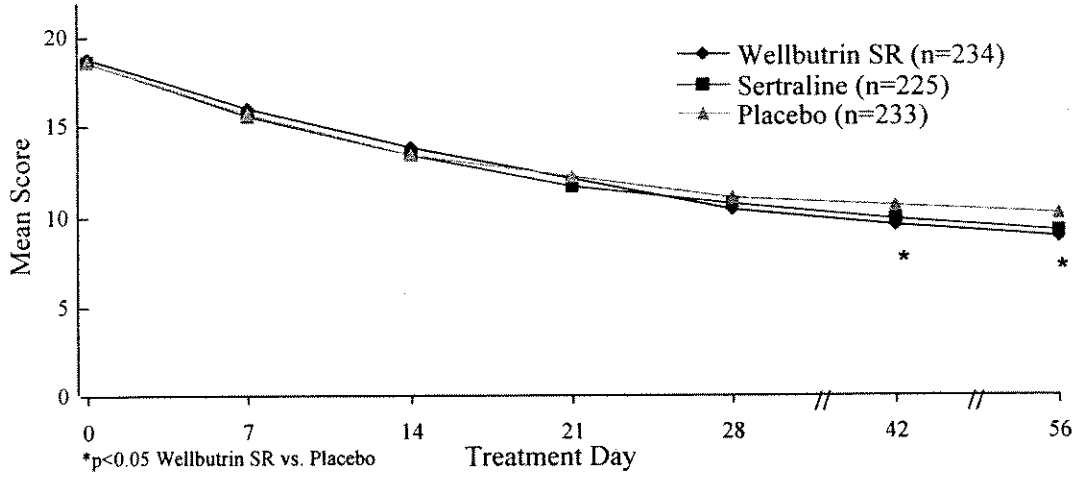
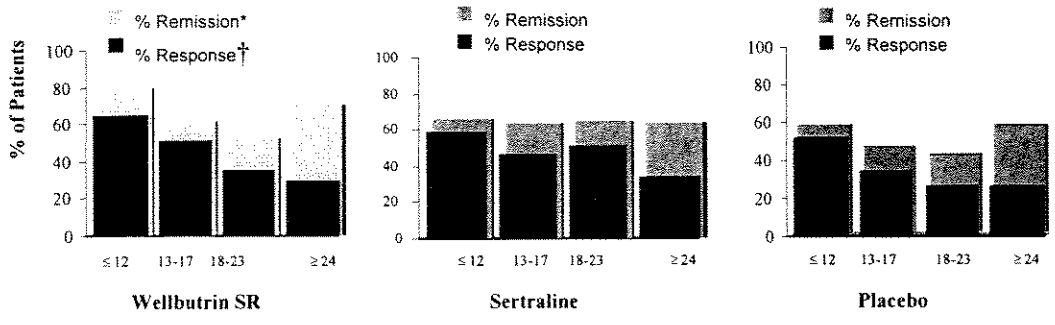


**Figure 2: Percentage of Patients Showing Response and Remission as a Function of Baseline HAM-A Score (22)**




* Remission defined as final HAM-$D_{21}$ score ≤ 8

† Response defined as final HAM-$D_{21}$ score ≥50% below baseline

**Baseline HAM-A**

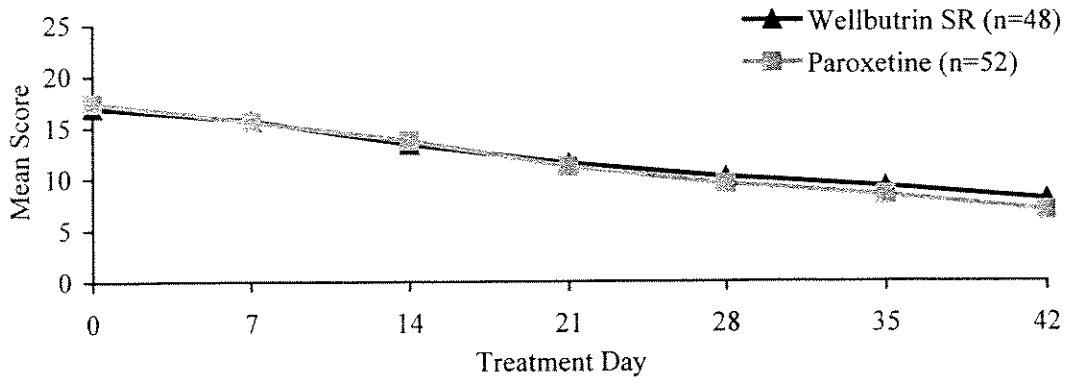
Retrospective review of this pooled data demonstrated no differences between Wellbutrin SR or sertraline in achieving anxiolysis in anxious depressed patients or in resolution of depressive symptoms regardless of the patient's baseline level of anxiety (22,23). They found no difference between groups in the median time (4 weeks) to reach a clinically significant anxiolytic effect (≥50% reduction in baseline HAM-A score)(23). Because severity of pretreatment anxiety did not predict preferential response to Wellbutrin SR or sertraline and did not distinguish responders to Wellbutrin SR from sertraline responders, the data indicate that degree of baseline anxiety should not be a basis for selecting between these treatments.

In a 16-week randomized acute phase treatment study, Rush et al (24) also conducted a retrospective review to determine if pretreatment anxiety levels were associated with preferential response to Wellbutrin SR (n=122) or sertraline (n=126). The results were consistent with previous findings which also suggest that pretreatment anxiety is unrelated to antidepressant response. They did not report any differences in the time to clinically significant anxiolysis between groups and did not differentiate between treatment responders.

**Wellbutrin SR versus paroxetine**

The efficacy and safety of Wellbutrin SR 100-300 mg/day and paroxetine 10-40 mg/day in elderly depressed outpatients were evaluated in a randomized, double-blind, controlled, 6-week trial (15). Wellbutrin SR and paroxetine were similarly efficacious for the treatment of depression and accompanying symptoms of anxiety. Analysis of HAM-A scores indicated a reduction in anxiety symptoms of approximately 50% for both Wellbutrin SR and paroxetine (Figure 4).

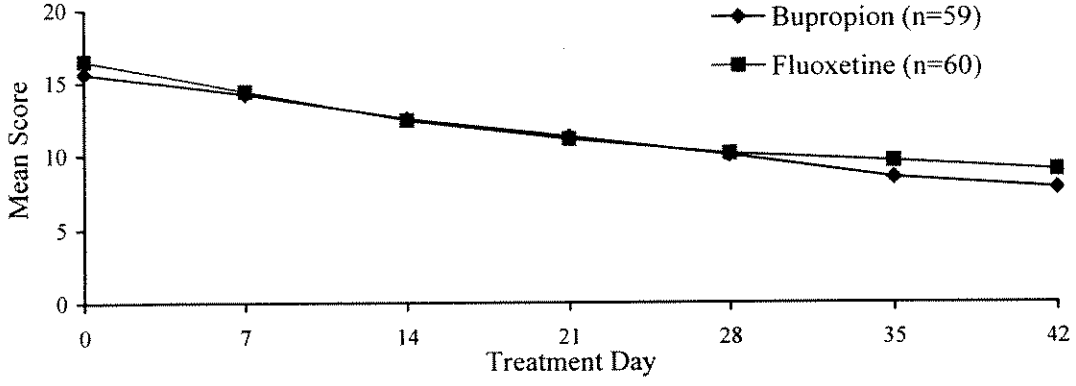
**Figure 4: Mean HAM-A Scores in Depressed Patients Treated with Wellbutrin SR or Paroxetine (15)**




**Wellbutrin SR versus fluoxetine**

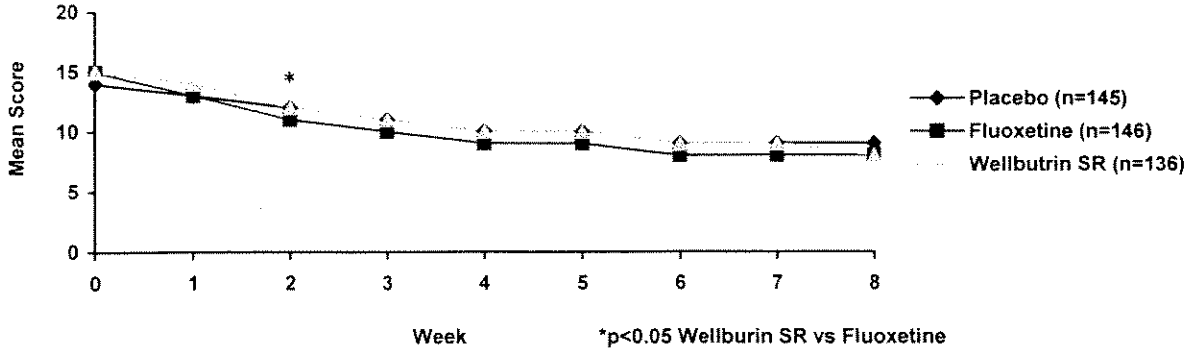
A double-blind trial comparing the immediate-release formulation of bupropion 225-450 mg/day and fluoxetine 20-80 mg/day in depressed outpatients also demonstrated similar efficacy and safety (14). Both treatments were associated with a significant improvement in symptoms of depression and accompanying symptoms of anxiety. From baseline to day 42, mean HAM-A scores for patients treated with bupropion decreased by 50% (15.6 to 7.8) compared with 45% (16.5 to 9.0) for patients treated with fluoxetine. There were no statistically significant differences between the bupropion and fluoxetine treatment groups on HAM-A scores at any treatment day (Figure 5).

**Figure 5: Mean HAM-A Scores in Depressed Patients Treated with Bupropion or Fluoxetine (13)**




The efficacy, effects on sexual functioning, and safety of Wellbutrin SR 150-400 mg/day and fluoxetine 20-60 mg/day were compared in two identical 8-week randomized, double-blind, placebo-controlled, multicenter trials (10,11,12). Wellbutrin SR, fluoxetine, and placebo demonstrated no differences between treatment groups in their effects on depression-related anxiety as measured by HAM-A scores at study endpoint (Figure 6).

**Figure 6: Mean HAM-A Scores in Depressed Patients Treated with Wellbutrin SR or Fluoxetine (10)**




**Treatment of anxiety disorders**

Open label clinical trials describe the successful use of bupropion in the treatment of post-traumatic stress disorder and social phobia. Although the immediate-release formulation of bupropion in doses up to 750 mg/day did not provide significant improvement in patients with panic disorder, the sustained-release formulation demonstrated significant changes from baseline in anticipatory anxiety and symptom severity.

*Post-traumatic stress disorder (PTSD)*

Almai et al evaluated the efficacy and tolerability of Wellbutrin SR for the treatment of civilian PTSD in an open-label clinical trial (n=13) (25). Male (n=2) and female (n=11) outpatients with a principle diagnosis of PTSD as a result of non-combat related trauma using DSM-IV criteria were included in the study. Comorbid diagnoses included dysthymia (n=8), major depression (n=1), and panic disorder (n=1). Wellbutrin SR was initiated at the dosage of 100 mg twice daily and increased to 150 mg twice daily by the second week if tolerated. Treatment duration was 9 weeks. Clinical response was defined as a 30% or greater improvement from baseline in the Clinician Administered PTSD Scale (CAPS) or the PTSD Checklist (PCL-C), or significant improvement in the Clinical Global Impression (CGI) Scale (defined as improvement of 2 or more units from baseline).

Eighty-nine percent (8/9) of completers met criteria. There was a marked improvement in core PTSD symptoms including re-experiencing, avoidance, numbing, and hyperarousal symptoms as assessed by CAPS ($p<0.001$) and PCL-C ($p<0.001$). CGI scores improved significantly from baseline to the end of treatment (5.2 to 2.9, $p<0.001$). Significant improvement was also seen in depressive symptoms as measured by scales for Hamilton Depression (HAM-D) ($p<0.001$) and Hamilton Anxiety (HAM-A) ($p<0.001$). Improvement began as early as week 2 of treatment with significant improvement by week 5. A 6-month follow-up on 4 subjects showed continued clinical improvement. Adverse events leading to discontinuation of therapy were due to rash (n=1), constipation (n=1), increased panic attacks (n=1), and positive urine test for cocaine (n=1).

Canive et al evaluated bupropion in the treatment of male combat veterans with chronic PTSD (n=17, average age of 51 years) in an open-label, 6-week clinical trial (26). Participants had either not received treatment with an antidepressant (n=6), had complained of side effects (n=3), or reported lack of efficacy with antidepressant therapy (n=8) prior to initiating bupropion. Eight participants (57%) also met diagnostic criteria for major depression. Dosing with the immediate-release formulation of bupropion

was initiated at 75mg bid and increased to 150mg bid after 2 weeks. After 4 weeks of bupropion administration, the dose could be increased to 400mg/day (200mg bid) or decreased to 200mg/day according to patient response and tolerability.

The mean daily dose of the immediate-release formulation of bupropion at the end of treatment was 295 mg/day (range 200-400mg/day). HAM-D and CAPS hyperarousal subscale scores decreased significantly from baseline to the 6-week follow-up visit ($p=0.0002$ and $p=0.016$, respectively). Ten (59%) patients were rated as "much" or "very much" improved on the CGI Improvement (CGI-I) scale. Marked decreases from baseline in HAM-A and total CAPS scores were reported although these changes were not statistically significant ($p=0.087$ and $p=0.055$, respectively). Additionally, CAPS did not detect a significant change in avoidance and intrusion symptoms. A major depression diagnosis did not relate significantly to score changes in the CAPS, HAM-D, or HAM-A. Bupropion was generally well tolerated in this study. Three patients who initiated bupropion after experiencing sexual dysfunction with SSRIs reported improvement in sexual functioning during bupropion therapy. Three patients (18%) discontinued bupropion due to adverse events including dizziness, change in thought patterns, loss of sleep, irritability, headache, sedation, loss of appetite, diarrhea, and stomach upset. The authors concluded that bupropion's major effect in this study was on depressive symptom improvement.

*Social phobia*

Emmanuel et al (27) evaluated 18 nondepressed patients with social phobia in a 12-week open-label trial with Wellbutrin SR. Efficacy measures included the Duke Brief Social Phobia Scale (BSPS), the Liebowitz Social Anxiety Scale (LSAS) and the Clinical Global Impressions of Improvement (CGI-I) and Severity (CGI-S) Scales. Response to treatment was defined as a CGI-I score of 1 or 2 (very much improved or much improved, respectively) and a $\geq$50% decrease in BSPS score.

Sixty percent of completers (6/10) were much or very much improved on the CGI-I Scale and 50% (5/10) had both a $\geq$50% decrease in BSPS score and were much or very much improved on the CGI-I. In addition, mean BSPS and LSAS scores improved significantly compared to baseline ($p<0.005$) on an intent-to-treat analysis (n=18). There were 6/18 responders on an intent-to-treat analysis. Two subjects were lost to follow-up and 5 subjects terminated early. Wellbutrin SR was generally well tolerated. Two patients discontinued due to an adverse event (jitteriness).

A case report in the published literature describes the use of the immediate-release formulation of bupropion in a 29 year old female with social phobia (28). The patient reported the onset of improvement 4 days after the initiation of bupropion. Symptoms continued to decrease rapidly and disappeared over the next few weeks at a dose of 300 mg daily. The only adverse events reported were a weight loss of 5 pounds and constipation.

*Panic disorder*

Emmanuel et al (29) evaluated the safety and efficacy of Wellbutrin SR for the treatment of panic disorder during an 8-week, open-label, flexible dose study. Subjects with a cormorbid diagnosis of major depression, bipolar disorder, psychosis, or substance use disorder were excluded from participating. Sixteen patients (4 men and 12 women) enrolled in the study and initiated Wellbutrin SR 50 mg/d with subsequent titration to a maximum of 400 mg/d. The study measured efficacy using the Clinical Global Impression scales for severity (CGI-S) and change (CGI-C), the Panic disorder severity scale (MC-PAS), total panic score, and safety with adverse experience assessments.

Twelve of the subjects who took more than two weeks of medication were considered evaluable. Symptom severity (CGI-S) scores decreased from 4.5±0.6 at baseline to 3.4±1.0 at the endpoint. Three of the 12 subjects were either "very much" or "much" improved on the CGI-C. The study reported a significant difference on the MC-PAS, with a mean change of 15.3±5.4 to 8.6±5.4. Full-blown panic attacks were found to decrease from 4.6±3.4 to 2.7±3.6, however statistical significance was not reached (p=0.169). The mean dose of Wellbutrin SR was 300 mg/day and was considered generally well-tolerated. Two subjects withdrew due from Wellbutrin SR due to adverse events. One subject developed stomach cramps and the other experienced an increase in anxiety and panic-like symptoms when the dose was increased to 300 mg/day or above.

Sheehan et al (30) reported the results of a placebo-controlled single-blind pilot study with bupropion in 12 outpatients with panic disorder and associated phobias. Flexible dosing of the immediate-release formulation of bupropion at 300-750 mg/day for at least 35 days was not associated with significant improvement of panic or phobic symptoms in any patient. Interpretation of the results of this study should include consideration of its small sample size and the utilization of the immediate-release formulation of bupropion above the maximum recommended daily dose of 450 mg.

The limited clinical experience with bupropion in patients with panic disorder may suggest potential efficacy. Additional clinical experience is necessary to define the role of bupropion in the treatment of anxiety disorders.

**REV1201**

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