The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: WELL AK130926

Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Effects on Sexual Functioning of Extended-Release Bupropion Hydrochloride (300-450mg) and Escitalopram (10-20mg) in Outpatients with Moderate to Severe Major Depression over an Eight-Week Treatment Period

Rationale: This study was conducted to assess the efficacy, safety, and effects on sexual functioning of an extended-release formulation (XL) of bupropion hydrochloride (BUP) that can be administered once daily (BUP XL), escitalopram, and placebo (PBO) in subjects being treated for moderate to severe major depression over an 8-week treatment period.

Phase: III

Study Period: 21 January 2003 – 15 June 2004

Study Design: Randomized, double-blind, double dummy, placebo-controlled, parallel group, multicenter

Centres: 22 centers in the United States

Indication: Major Depressive Disorder (MDD)

Treatment: BUP XL or matching placebo tablet was administered at doses of 150mg/day during Week 1, 300mg/day from Week 2 through Week 4, and either 300mg/day, or if clinically indicated, 450mg/day from Week 5 through Week 8. Escitalopram or matching placebo capsule was administered at doses of 10mg/day for the first 4 weeks and either 10mg/day, or if clinically indicated, 20mg/day from Week 5 through Week 8.

Objectives: The primary objectives were to compare the effects of BUP XL versus escitalopram on orgasm based on investigator interview and antidepressant efficacy versus PBO based on change in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score.

Primary Outcome/Efficacy Variable: The primary endpoints were the percentage of subjects with orgasm dysfunction based on investigators' interviews and the mean change from randomization to Week 8 (LOCF) in HAMD-17 total score.

Secondary Outcome/Efficacy Variable(s): Key secondary endpoints were: the percentage of subjects with worsened sexual function at Week 8 (or study exit); the percentage of subjects with sexual desire disorder at Week 8 (or study exit); the percentage of subjects in remission (HAMD-17 total score $\leq$7) at Week 8 (or study exit); the percentage of subjects who were satisfied with their sexual functioning at Week 8 (or study exit) who had reported being satisfied with their sexual functioning at randomization.

Statistical Methods: Efficacy results are presented for the intent-to-treat (ITT) population, using the LOCF technique unless otherwise noted. Between-treatment group comparisons of the proportion of subjects with orgasmic dysfunction at Week 8 (LOCF) and other categorical measures were done using the Cochran-Mantel-Haenszel test controlling for center and gender. Continuous measures such as change from randomization to end of treatment in HAMD-17 total score at Week 8 (LOCF) were examined using analysis of covariance (ANCOVA) with value at randomization as a covariate and centre, gender, and treatment as fixed effects. Efficacy of the active treatment groups was compared by computing 95% confidence intervals for the mean difference between the two active treatment groups (BUP XL versus escitalopram) for changes from randomization to Week 8 in HAMD-17 total score and Clinical Global Impression Severity of Illness score (CGI-S) at Week 8 (LOCF) using ANCOVA.

Study Population: Male and female subjects at least 18 years of age with a primary diagnosis of MDD, based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM IV), with a minimum score of 19 on the HAMD-17 scale and a duration of the current episode of depression of between 12 weeks to 2 years, and sexual activity leading to orgasm at least once every 2 weeks could qualify for study entry.

	BUP XL	**Escitalopram**	**PBO**
Number of Subjects:			
Planned, N	140	140	140
Entered, N	138	149	137
Entered and Included in Analyses, N	135	144	132
Completed, n (%)	99 (73)	105 (73)	105 (80)
Total Number Subjects Withdrawn, N (%)	36 (27)	38 (27)	27 (20)
Withdrawn due to Adverse Events, n (%)	13 (10)	5 (3)	6 (5)
Withdrawn due to Lack of Efficacy, n (%)	-	-	-
Withdrawn for other reasons n (%)	23 (17)	33 (23)	21 (16)
13 subjects from Center 009583 were excluded from analyses after deviations from Good Clinical Practice were noted			

during a routine site audit.			
Demographics:	**BUP XL**	**Escitalopram**	**PBO**
N (Safety)	135	143	132
Females: Males	76:59	78:65	76:56
Mean Age, years (sd)	37.0 (12.5)	35.7 (12.1)	37.0 (10.7)
White, n (%)	97 (72)	103 (72)	99 (75)
Primary Results: ITT Population	**BUP XL N=129**	**Escitalopram N=133**	**PBO N=126**
Subjects with orgasm dysfunction at Week 8, n (%)	21 (16)	38 (29)	10 (8)
Treatment Comparisons	p-value		
BUP XL vs escitalopram	0.014		
BUP XL vs PBO	0.094		
Escitalopram vs PBO	<0.001		
Change from randomization to Week 8 in HAMD-17 total score (LOCF), Least square mean (SE)	-13.1 (0.7)	-12.9 (0.7)	-11.9 (0.7)
Between treatment group comparisons	p-value		
BUP XL vs escitalopram	0.833		
95% Confidence Interval	(-1.9, 1.6)		
Between treatment group comparisons	p-values		
BUP XL vs PBO	0.179		
Escitalopram vs PBO	0.252		
Secondary Results:	**BUP XL N=129**	**Escitalopram N=133**	**PBO N=126**
Subjects with Worsened Sexual Functioning Compared to Randomization (LOCF) - ITT			
Week 8, n	129	132	125
Worsened, n (%)	28 (22)	45 (34)	20 (16)
Subjects with Sexual Desire Disorder			
Baseline, n (%)	8 (6)	6 (5)	4 (3)
Week 8 (LOCF), n (%)	13 (10)	27 (20)	14 (11)
Subjects Satisfied with Overall Sexual Functioning at Week 8 who were satisfied at randomization			
Baseline, n	115	117	110
Week 8 **(**LOCF), n (%)	107 (93)	92 (79)	100 (91)
Proportions of HAMD-17 Remitters (Score of ≤7) at Week 8 - ITT			
Baseline, n	0	0	0
Week 8 (LOCF), n (%)	59 (46)	56 (42)	48 (38)
Safety Results: All subjects who received at least one dose of study drug were included in the safety analysis.			
Most Frequent Adverse Events – On-Therapy	**BUP XL N=132**	**Escitalopram N=135**	**PBO N=143**
Subjects with any AE(s), n (%)	109 (81)	113 (79)	102 (77)
Headache	33 (24)	37 (26)	38 (29)
Dry Mouth	30 (22)	18 (13)	17 (13)
Nausea	17 (13)	22 (15)	14 (11)
Constipation	15 (11)	5 (3)	9 (7)
Dizziness	13 (10)	8 (6)	5 (4)
Insomnia[1]	18 (13)	12 (8)	14 (11)
Diarrhea	10 (7)	15 (10)	12 (9)
Fatigue	7 (5)	28 (20)	7 (5)
Abdominal Pain - Upper	6 (4)	5 (3)	1 (<1)
Tremor	6 (4)	3 (2)	2 (2)
Irritability	6 (4)	0	6 (5)
Dyspepsia	5 (4)	5 (3)	12 (9)

Flatulence	4 (3)	8 (6)	3 (2)
Somnolence	4 (3)	11 (8)	8 (6)
Palpitations	4 (3)	3 (2)	6 (5)
Upper Respiratory Tract Infection	3 (2)	8 (6)	5 (4)
Toothache	2 (1)	3 (2)	6 (5)
Back Pain	2 (1)	6 (4)	6 (5)
Sinus Congestion	2 (1)	4 (3)	6 (5)
Yawning	1 (<1)	8 (6)	0
Stomach Discomfort	0	0	6 (5)
Pain in Extremity	0	2 (1)	6 (5)
[1]Includes insomnia, initial insomnia, middle insomnia and early morning awakening.			
Serious Adverse Events - On-Therapy and Post-Treatment n (%) [n considered by the investigator to be related to study medication]	**BUP XL N=135**	**Escitalopram N=143**	**PBO N=132**
Subjects with non-fatal SAEs, n (%)	2 (1.5)	1 (<1)	0
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Accidental Overdose	1 (<1) [0]	0	0
Endometriosis (3 days after last dose)	1 (<1) [0]	0	0
Agitation	0	1 (<1) [0]	0
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Subjects with fatal SAEs, n (%)	0	0	0
Conclusion: See publication below.			
Publications: Clayton A, Wightman D, Horrigan JP, Modell JG, Richard NE, Krishen A. A comparison of the effects on sexual functioning of bupropion XL, escitalopram and placebo in outpatients with major depression. 17th Annual US Psychiatric & Mental Health Congress, San Diego, CA, 18-21 November, 2004, Abstract No. 105 Clayton AH, Croft H, Horrigan JP, Wightman DS, Krishen A, Richard NE, Modell JG. Bupropion XL compared with escitalopram: effects on sexual functioning and antidepressant efficacy in two randomized, double-blind, placebo-controlled studies. *J Clin Psychiatry 2006; 67:736-746*			

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