

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-592/S-018

Name: Zyprexa Tablets

Generic Name: olanzapine

Sponsor: Eli Lilly and Company

Approval Date: 07/10/2003

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**APPLICATION NUMBER:
NDA 20-592/S-018**

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APPROVAL LETTER



NDA 20-592 / S-018

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285
USA

Dear Dr. Brophy:

Please refer to your supplemental new drug application (NDA) dated September 16, 2002, received September 17, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, and 20 mg. This supplemental NDA provides for the use of olanzapine in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder.

We also acknowledge receipt of your amendments dated September 26, 2002 and November 13, 2002 (FAX).

Approval of Supplemental Application with Agreed-Upon Labeling Text (Enclosed)

We have completed the review of this application as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed agreed-upon labeling text (package insert). Accordingly, this application is approved, effective on the date of this letter.

Submission of Final Printed Labeling (FPL)

The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling text for the package insert. Please submit the FPL electronically according to the Guidance for Industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please mount individually ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL For Approved Supplement NDA 20-592/S-018" regardless of the medium chosen for its submission (paper or electronic). FDA approval of this additional submission of FPL is not required before the labeling is used.

CMC: Categorical Exclusion

We have completed our review of the information provided by your firm, and we agree with your request for a Categorical Exclusion from the requirement to perform a full Environmental Assessment for this application.

Pediatric Rule: Pediatric Waiver Request

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] has been challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule

and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, intervening third parties have decided to appeal the court's decision striking down the rule.

We note Lilly's ongoing commitment to the conduct of a pediatric study of olanzapine as monotherapy in adolescent patients diagnosed with manic or mixed episodes associated with bipolar I disorder (with or without psychotic features). We also note that on May 30, 2002, which predates the court ruling on the Pediatric Rule, the Division granted Lilly a waiver from the then-existing requirement to conduct pediatric studies of olanzapine in combination with lithium or valproate. The Division has determined that this waiver would be upheld if the Pediatric Rule is upheld or a similar rule enacted.

However, the pediatric exclusivity provisions of FDAMA, as reauthorized by the Best Pharmaceuticals for Children Act, are not affected by the court ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on the FDA Web site at www.fda.gov/cder/pediatric) for details.

If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request to as being responsive to the Written Request. Applicants should therefore obtain a Written Request before submitting such pediatric studies to an NDA.

Promotional Materials

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. Please submit all material in draft or mock-up form rather than final printed format. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

"Dear Health Care Professional" Letters

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Agreed-Upon Labeling)
[The electronic signature page will follow the labeling.]

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz

7/10/03 03:02:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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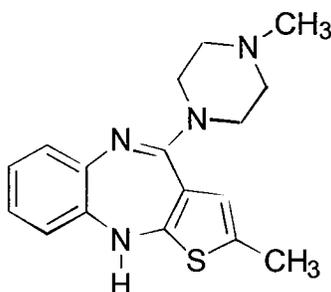
FINAL PRINTED LABELING

ZYPREXA[®]
(Olanzapine) Tablets

ZYPREXA[®] ZYDIS[®]
(Olanzapine) Orally Disintegrating Tablets

DESCRIPTION

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is C₁₇H₂₀N₄S, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), 10 mg (32 μmol), 15 mg (48 μmol), or 20 mg (64 μmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5.0, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μmol), 10 mg (32 μmol), 15 mg (48 μmol) or 20 mg (64 μmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin 5HT_{2A/2C} (K_i=4 and 11 nM, respectively), dopamine D₁₋₄ (K_i=11-31 nM), muscarinic M₁₋₅ (K_i=1.9-25 nM), histamine H₁ (K_i=7 nM), and adrenergic α₁ receptors (K_i=19 nM). Olanzapine binds weakly to GABA_A, BZD, and β adrenergic receptors (K_i>10 μM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT₂) antagonism. The mechanism of

37 action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is
38 unknown.

39 Antagonism at receptors other than dopamine and 5HT₂ with similar receptor affinities may
40 explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of
41 muscarinic M₁₋₅ receptors may explain its anticholinergic effects. Olanzapine's antagonism of
42 histamine H₁ receptors may explain the somnolence observed with this drug. Olanzapine's
43 antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this
44 drug.

45 **Pharmacokinetics**

46 Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours
47 following an oral dose. It is eliminated extensively by first pass metabolism, with approximately
48 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the
49 rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets
50 and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are
51 bioequivalent.

52 Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to
53 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to
54 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

55 Administration of olanzapine once daily leads to steady-state concentrations in about one week
56 that are approximately twice the concentrations after single doses. Plasma concentrations, half-life,
57 and clearance of olanzapine may vary between individuals on the basis of smoking status, gender,
58 and age (*see Special Populations*).

59 Olanzapine is extensively distributed throughout the body, with a volume of distribution of
60 approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to
61 1100 ng/mL, binding primarily to albumin and α_1 -acid glycoprotein.

62 Metabolism and Elimination — Following a single oral dose of ¹⁴C labeled olanzapine, 7% of
63 the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is
64 highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and
65 feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total
66 radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major
67 circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the
68 concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the
69 concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations
70 observed.

71 Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary
72 metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the
73 flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated
74 oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is
75 not reduced in subjects who are deficient in this enzyme.

76 **Special Populations**

77 Renal Impairment — Because olanzapine is highly metabolized before excretion and only 7% of
78 the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the
79 pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar
80 in patients with severe renal impairment and normal subjects, indicating that dosage adjustment
81 based upon the degree of renal impairment is not required. In addition, olanzapine is not removed
82 by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

83 Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce
84 the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with

85 clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the
86 pharmacokinetics of olanzapine.

87 Age — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was
88 about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤65 years). Caution
89 should be used in dosing the elderly, especially if there are other factors that might additively
90 influence drug metabolism and/or pharmacodynamic sensitivity (*see* DOSAGE AND
91 ADMINISTRATION).

92 Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There
93 were, however, no apparent differences between men and women in effectiveness or adverse
94 effects. Dosage modifications based on gender should not be needed.

95 Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers,
96 although dosage modifications are not routinely recommended.

97 Race — No specific pharmacokinetic study was conducted to investigate the effects of race. A
98 cross-study comparison between data obtained in Japan and data obtained in the US suggests that
99 exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are
100 administered. Clinical trial safety and efficacy data, however, did not suggest clinically significant
101 differences among Caucasian patients, patients of African descent, and a third pooled category
102 including Asian and Hispanic patients. Dosage modifications for race are, therefore, not
103 recommended.

104 Combined Effects — The combined effects of age, smoking, and gender could lead to substantial
105 pharmacokinetic differences in populations. The clearance in young smoking males, for example,
106 may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be
107 necessary in patients who exhibit a combination of factors that may result in slower metabolism of
108 olanzapine (*see* DOSAGE AND ADMINISTRATION).

109 For specific information about the pharmacology of lithium or valproate, refer to the CLINICAL
110 PHARMACOLOGY section of the package inserts for these other products.

111 **Clinical Efficacy Data**

112 **Schizophrenia**

113 The efficacy of olanzapine in the treatment of schizophrenia was established in 2 short-term
114 (6-week) controlled trials of inpatients who met DSM III-R criteria for schizophrenia. A
115 single haloperidol arm was included as a comparative treatment in one of the two trials, but this
116 trial did not compare these two drugs on the full range of clinically relevant doses for both.

117 Several instruments were used for assessing psychiatric signs and symptoms in these studies,
118 among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general
119 psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The
120 BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and
121 unusual thought content) is considered a particularly useful subset for assessing actively psychotic
122 schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI),
123 reflects the impression of a skilled observer, fully familiar with the manifestations of
124 schizophrenia, about the overall clinical state of the patient. In addition, two more recently
125 developed but less well evaluated scales were employed; these included the 30-item Positive and
126 Negative Symptoms Scale (PANSS), in which is embedded the 18 items of the BPRS, and the
127 Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the
128 following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative
129 subscale or SANS; and CGI Severity. The results of the trials follow:

130 (1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and
131 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to
132 placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis
133 cluster, on the PANSS Negative subscale, and on CGI Severity.

134 (2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine
 135 (5.0 ± 2.5 mg/day, 10.0 ± 2.5 mg/day, and 15.0 ± 2.5 mg/day) on a once daily schedule, the
 136 two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were
 137 superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the
 138 highest olanzapine dose group was superior to placebo on the SANS. There was no clear
 139 advantage for the high dose group over the medium dose group.

140 Examination of population subsets (race and gender) did not reveal any differential
 141 responsiveness on the basis of these subgroupings.

142 In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for
 143 schizophrenia and who remained stable on olanzapine during open label treatment for at least
 144 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to
 145 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms
 146 of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however,
 147 criteria were met for stopping the trial early due to an excess of placebo relapses compared to
 148 olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary
 149 outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in
 150 patients stabilized for approximately 8 weeks and followed for an observation period of up to
 151 8 months.

152 **Bipolar Mania**

153 Monotherapy — The efficacy of olanzapine in the treatment of acute manic episodes was
 154 established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in patients who
 155 met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials
 156 included patients with or without psychotic features and with or without a rapid-cycling course.

157 The primary rating instrument used for assessing manic symptoms in these trials was the Young
 158 Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the
 159 degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated
 160 mood, speech, increased activity, sexual interest, language/thought disorder, thought content,
 161 appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The
 162 primary outcome in these trials was change from baseline in the Y-MRS total score. The results of
 163 the trials follow:

164 (1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine
 165 (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the
 166 reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the
 167 first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size
 168 and site variability, was not shown to be superior to placebo on this outcome.

169 (2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine
 170 (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the
 171 reduction of Y-MRS total score.

172 Combination Therapy — The efficacy of olanzapine with concomitant lithium or valproate in the
 173 treatment of acute manic episodes was established in two controlled trials in patients who met the
 174 DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included
 175 patients with or without psychotic features and with or without a rapid-cycling course. The results
 176 of the trials follow:

177 (1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate
 178 therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥ 16) were randomized to
 179 receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a
 180 dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate
 181 (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 μ g/mL to 125 μ g/mL, respectively) was
 182 superior to lithium or valproate alone in the reduction of Y-MRS total score.

183 (2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or
 184 valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥ 16) were
 185 randomized to receive either olanzapine or placebo, in combination with their original therapy.
 186 Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with
 187 lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 $\mu\text{g/mL}$ to 125 $\mu\text{g/mL}$,
 188 respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

189

INDICATIONS AND USAGE

190 Schizophrenia

191 ZYPREXA is indicated for the treatment of schizophrenia.

192 The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of
 193 schizophrenic inpatients (*see* CLINICAL PHARMACOLOGY).

194 The effectiveness of oral ZYPREXA at maintaining a treatment response in schizophrenic
 195 patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed
 196 for a period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL
 197 PHARMACOLOGY). Nevertheless, the physician who elects to use ZYPREXA for extended
 198 periods should periodically re-evaluate the long-term usefulness of the drug for the individual
 199 patient (*see* DOSAGE AND ADMINISTRATION).

200 Bipolar Mania

201 Monotherapy — ZYPREXA is indicated for the short-term treatment of acute manic episodes
 202 associated with Bipolar I Disorder.

203 The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and
 204 one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently
 205 displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL
 206 PHARMACOLOGY).

207 Combination Therapy — The combination of ZYPREXA with lithium or valproate is indicated
 208 for the short-term treatment of acute manic episodes associated with Bipolar I Disorder.

209 The efficacy of ZYPREXA in combination with lithium or valproate was established in
 210 two placebo-controlled (6-week) trials with patients meeting DSM-IV criteria for Bipolar I
 211 Disorder who currently displayed an acute manic or mixed episode with or without psychotic
 212 features (*see* CLINICAL PHARMACOLOGY).

213 The effectiveness of ZYPREXA for longer-term use, that is, for more than 6 weeks' treatment of
 214 an acute episode, and for prophylactic use in mania, has not been systematically evaluated in
 215 controlled clinical trials. Therefore, physicians who elect to use ZYPREXA for extended periods
 216 should periodically re-evaluate the long-term risks and benefits of the drug for the individual
 217 patient (*see* DOSAGE AND ADMINISTRATION).

218

CONTRAINDICATIONS

219 ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.

220 For specific information about the contraindications of lithium or valproate, refer to the
 221 CONTRAINDICATIONS section of the package inserts for these other products.

222

WARNINGS

223 Neuroleptic Malignant Syndrome (NMS) — A potentially fatal symptom complex sometimes
 224 referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with
 225 administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are
 226 hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability
 227 (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional
 228 signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute
 229 renal failure.

230 The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a
231 diagnosis, it is important to exclude cases where the clinical presentation includes both serious
232 medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated
233 extrapyramidal signs and symptoms (EPS). Other important considerations in the differential
234 diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central
235 nervous system pathology.

236 The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs
237 and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical
238 monitoring; and 3) treatment of any concomitant serious medical problems for which specific
239 treatments are available. There is no general agreement about specific pharmacological treatment
240 regimens for NMS.

241 If a patient requires antipsychotic drug treatment after recovery from NMS, the potential
242 reintroduction of drug therapy should be carefully considered. The patient should be carefully
243 monitored, since recurrences of NMS have been reported.

244 Tardive Dyskinesia — A syndrome of potentially irreversible, involuntary, dyskinetic
245 movements may develop in patients treated with antipsychotic drugs. Although the prevalence of
246 the syndrome appears to be highest among the elderly, especially elderly women, it is impossible
247 to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which
248 patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their
249 potential to cause tardive dyskinesia is unknown.

250 The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are
251 believed to increase as the duration of treatment and the total cumulative dose of antipsychotic
252 drugs administered to the patient increase. However, the syndrome can develop, although much
253 less commonly, after relatively brief treatment periods at low doses.

254 There is no known treatment for established cases of tardive dyskinesia, although the syndrome
255 may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic
256 treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the
257 syndrome and thereby may possibly mask the underlying process. The effect that symptomatic
258 suppression has upon the long-term course of the syndrome is unknown.

259 Given these considerations, olanzapine should be prescribed in a manner that is most likely to
260 minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be
261 reserved for patients (1) who suffer from a chronic illness that is known to respond to
262 antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful
263 treatments are not available or appropriate. In patients who do require chronic treatment, the
264 smallest dose and the shortest duration of treatment producing a satisfactory clinical response
265 should be sought. The need for continued treatment should be reassessed periodically.

266 If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug
267 discontinuation should be considered. However, some patients may require treatment with
268 olanzapine despite the presence of the syndrome.

269 For specific information about the warnings of lithium or valproate, refer to the WARNINGS
270 section of the package inserts for these other products.

271

PRECAUTIONS

272 **General**

273 Orthostatic Hypotension — Olanzapine may induce orthostatic hypotension associated with
274 dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration
275 period, probably reflecting its α_1 -adrenergic antagonistic properties. Syncope was reported in
276 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 studies. The risk of orthostatic
277 hypotension and syncope may be minimized by initiating therapy with 5 mg QD (*see* DOSAGE
278 AND ADMINISTRATION). A more gradual titration to the target dose should be considered if

279 hypotension occurs. Olanzapine should be used with particular caution in patients with known
280 cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction
281 abnormalities), cerebrovascular disease, and conditions which would predispose patients to
282 hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

283 Seizures — During premarketing testing, seizures occurred in 0.9% (22/2500) of
284 olanzapine-treated patients. There were confounding factors that may have contributed to the
285 occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients
286 with a history of seizures or with conditions that potentially lower the seizure threshold,
287 e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a
288 population of 65 years or older.

289 Hyperprolactinemia — As with other drugs that antagonize dopamine D₂ receptors, olanzapine
290 elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue
291 culture experiments indicate that approximately one-third of human breast cancers are prolactin
292 dependent in vitro, a factor of potential importance if the prescription of these drugs is
293 contemplated in a patient with previously detected breast cancer of this type. Although
294 disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported
295 with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is
296 unknown for most patients. As is common with compounds which increase prolactin release, an
297 increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies
298 conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor
299 epidemiologic studies have shown an association between chronic administration of this class of
300 drugs and tumorigenesis in humans; the available evidence is considered too limited to be
301 conclusive.

302 Transaminase Elevations — In placebo-controlled studies, clinically significant ALT (SGPT)
303 elevations (≥ 3 times the upper limit of the normal range) were observed in 2% (6/243) of patients
304 exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients
305 experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite
306 continued treatment and in two others, enzymes decreased upon discontinuation of olanzapine. In
307 the remaining two patients, one, seropositive for hepatitis C, had persistent enzyme elevation for
308 four months after discontinuation, and the other had insufficient follow-up to determine if enzymes
309 normalized.

310 Within the larger premarketing database of about 2400 patients with baseline SGPT ≤ 90 IU/L,
311 the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients
312 experienced jaundice or other symptoms attributable to liver impairment and most had transient
313 changes that tended to normalize while olanzapine treatment was continued.

314 Among all 2500 patients in clinical trials, about 1% (23/2500) discontinued treatment due to
315 transaminase increases.

316 Caution should be exercised in patients with signs and symptoms of hepatic impairment, in
317 patients with pre-existing conditions associated with limited hepatic functional reserve, and in
318 patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of
319 transaminases is recommended in patients with significant hepatic disease (*see* Laboratory Tests).

320 Potential for Cognitive and Motor Impairment — Somnolence was a commonly reported adverse
321 event associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine
322 patients compared to 15% in placebo patients. This adverse event was also dose related.
323 Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

324 Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should
325 be cautioned about operating hazardous machinery, including automobiles, until they are
326 reasonably certain that olanzapine therapy does not affect them adversely.

327 Body Temperature Regulation — Disruption of the body's ability to reduce core body
328 temperature has been attributed to antipsychotic agents. Appropriate care is advised when

329 prescribing olanzapine for patients who will be experiencing conditions which may contribute to
330 an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat,
331 receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

332 **Dysphagia** — Esophageal dysmotility and aspiration have been associated with antipsychotic
333 drug use. Two olanzapine-treated patients (2/407) in two studies in patients with Alzheimer's
334 disease died from aspiration pneumonia during or within 30 days of the termination of the
335 double-blind portion of their respective studies; there were no deaths in the placebo-treated
336 patients. One of these patients had experienced dysphagia prior to the development of aspiration
337 pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in patients with
338 advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used
339 cautiously in patients at risk for aspiration pneumonia.

340 **Suicide** — The possibility of a suicide attempt is inherent in schizophrenia and in bipolar
341 disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions
342 for olanzapine should be written for the smallest quantity of tablets consistent with good patient
343 management, in order to reduce the risk of overdose.

344 **Use in Patients with Concomitant Illness** — Clinical experience with olanzapine in patients with
345 certain concomitant systemic illnesses (*see* Renal Impairment and Hepatic Impairment *under*
346 CLINICAL PHARMACOLOGY, Special Populations) is limited.

347 Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with
348 olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse
349 events possibly related to cholinergic antagonism. Such adverse events were not often the basis for
350 discontinuations from olanzapine, but olanzapine should be used with caution in patients with
351 clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

352 In a fixed-dose study of olanzapine (olanzapine at doses of 5, 10, and 15 mg/day) and placebo in
353 nursing home patients (mean age: 83 years, range: 61-97; median Mini-Mental State
354 Examination (MMSE): 5, range: 0-22) having various psychiatric symptoms in association with
355 Alzheimer's disease, the following treatment-emergent adverse events were reported in all (each
356 and every) olanzapine-treated groups at an incidence of either (1) two-fold or more in excess of
357 the placebo-treated group, where at least 1 placebo-treated patient was reported to have
358 experienced the event, or (2) at least 2 cases if no placebo-treated patient was reported to have
359 experienced the event: somnolence, abnormal gait, fever, dehydration, and back pain. The rate of
360 discontinuation in this study for olanzapine was 12% vs 4% with placebo. Discontinuations due to
361 abnormal gait (1% for olanzapine vs 0% for placebo), accidental injury (1% for olanzapine vs
362 0% for placebo), and somnolence (3% for olanzapine vs 0% for placebo) were considered to be
363 drug related. As with other CNS-active drugs, olanzapine should be used with caution in elderly
364 patients with dementia (*see* PRECAUTIONS).

365 Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent
366 history of myocardial infarction or unstable heart disease. Patients with these diagnoses were
367 excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with
368 olanzapine, caution should be observed in cardiac patients (*see* Orthostatic Hypotension).

369 For specific information about the precautions of lithium or valproate, refer to the
370 PRECAUTIONS section of the package inserts for these other products.

371 **Information for Patients**

372 Physicians are advised to discuss the following issues with patients for whom they prescribe
373 olanzapine:

374 **Orthostatic Hypotension** — Patients should be advised of the risk of orthostatic hypotension,
375 especially during the period of initial dose titration and in association with the use of concomitant
376 drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol (*see* Drug
377 Interactions).

378 Interference with Cognitive and Motor Performance — Because olanzapine has the potential to
379 impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous
380 machinery, including automobiles, until they are reasonably certain that olanzapine therapy does
381 not affect them adversely.

382 Pregnancy — Patients should be advised to notify their physician if they become pregnant or
383 intend to become pregnant during therapy with olanzapine.

384 Nursing — Patients should be advised not to breast-feed an infant if they are taking olanzapine.

385 Concomitant Medication — Patients should be advised to inform their physicians if they are
386 taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for
387 interactions.

388 Alcohol — Patients should be advised to avoid alcohol while taking olanzapine.

389 Heat Exposure and Dehydration — Patients should be advised regarding appropriate care in
390 avoiding overheating and dehydration.

391 Phenylketonurics — ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains
392 phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively).

393 **Laboratory Tests**

394 Periodic assessment of transaminases is recommended in patients with significant hepatic
395 disease (*see* Transaminase Elevations).

396 **Drug Interactions**

397 The risks of using olanzapine in combination with other drugs have not been extensively
398 evaluated in systematic studies. Given the primary CNS effects of olanzapine, caution should be
399 used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

400 Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain
401 antihypertensive agents.

402 Olanzapine may antagonize the effects of levodopa and dopamine agonists.

403 The Effect of Other Drugs on Olanzapine — Agents that induce CYP1A2 or glucuronyl
404 transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine
405 clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although
406 olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme
407 may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a
408 dosage decrease (for inhibition) may need to be considered with specific drugs.

409 Charcoal — The administration of activated charcoal (1 g) reduced the C_{max} and AUC of
410 olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours
411 after dosing, charcoal may be a useful treatment for olanzapine overdose.

412 Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and
413 magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

414 Carbamazepine — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase
415 in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent
416 inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater
417 increase in olanzapine clearance.

418 Ethanol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine
419 pharmacokinetics.

420 Fluoxetine — Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean
421 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in
422 olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the
423 overall variability between individuals, and therefore dose modification is not routinely
424 recommended.

425 Fluvoxamine — Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This
426 results in a mean increase in olanzapine C_{max} following fluvoxamine of 54% in female
427 nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%,
428 respectively. Lower doses of olanzapine should be considered in patients receiving concomitant
429 treatment with fluvoxamine.

430 Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

431 Effect of Olanzapine on Other Drugs — In vitro studies utilizing human liver microsomes suggest
432 that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and
433 CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by
434 these enzymes.

435 Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of
436 lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of
437 lithium.

438 Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little
439 potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate
440 has little effect on the metabolism of olanzapine in vitro. In vivo administration of olanzapine
441 (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate.
442 Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

443 Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active
444 metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics
445 of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the
446 co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic
447 hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the
448 pharmacokinetics of theophylline or its metabolites.

449 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

450 Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine
451 was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent
452 to 0.8-5 times the maximum recommended human daily dose on a mg/m² basis) and 0.25, 2,
453 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily dose on a mg/m²
454 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4,
455 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human
456 daily dose on a mg/m² basis, respectively). The incidence of liver hemangiomas and
457 hemangiosarcomas was significantly increased in one mouse study in female mice dosed at
458 8 mg/kg/day (2 times the maximum recommended human daily dose on a mg/m² basis). These
459 tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day
460 (2-5 times the maximum recommended human daily dose on a mg/m² basis); in this study, there
461 was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of
462 mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed
463 at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum
464 recommended human daily dose on a mg/m² basis, respectively). Antipsychotic drugs have been
465 shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not
466 measured during the olanzapine carcinogenicity studies; however, measurements during subchronic
467 toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the
468 same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been
469 found in rodents after chronic administration of other antipsychotic drugs and is considered to be
470 prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine
471 tumors in rodents is unknown (*see Hyperprolactinemia under PRECAUTIONS, General*).

472 Mutagenesis — No evidence of mutagenic potential for olanzapine was found in the Ames
473 reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in

474 Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of
475 forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone
476 marrow of Chinese hamsters.

477 **Impairment of Fertility** — In a fertility and reproductive performance study in rats, male mating
478 performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was
479 decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily
480 dose on a mg/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects
481 on male mating performance. In female rats, the precoital period was increased and the mating
482 index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily dose on a mg/m²
483 basis). Diestrus was prolonged and estrus delayed at 1.1 mg/kg/day (0.6 times the maximum
484 recommended human daily dose on a mg/m² basis); therefore olanzapine may produce a delay in
485 ovulation.

486 **Pregnancy**

487 **Pregnancy Category C** — In reproduction studies in rats at doses up to 18 mg/kg/day and in
488 rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily dose
489 on a mg/m² basis, respectively) no evidence of teratogenicity was observed. In a rat teratology
490 study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of
491 18 mg/kg/day (9 times the maximum recommended human daily dose on a mg/m² basis). Gestation
492 was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily dose on a mg/m²
493 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and
494 decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the
495 maximum recommended human daily dose on a mg/m² basis).

496 Placental transfer of olanzapine occurs in rat pups.

497 There are no adequate and well-controlled trials with olanzapine in pregnant females.
498 Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in
499 normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions,
500 and 1 spontaneous abortion. Because animal reproduction studies are not always predictive of
501 human response, this drug should be used during pregnancy only if the potential benefit justifies the
502 potential risk to the fetus.

503 **Labor and Delivery**

504 Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery
505 in humans is unknown.

506 **Nursing Mothers**

507 Olanzapine was excreted in milk of treated rats during lactation. It is not known if olanzapine is
508 excreted in human milk. It is recommended that women receiving olanzapine should not
509 breast-feed.

510 **Pediatric Use**

511 Safety and effectiveness in pediatric patients have not been established.

512 **Geriatric Use**

513 Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263) were 65 years
514 of age or over. In patients with schizophrenia, there was no indication of any different tolerability
515 of olanzapine in the elderly compared to younger patients. Studies in patients with various
516 psychiatric symptoms in association with Alzheimer's disease have suggested that there may be a
517 different tolerability profile in this population compared to younger patients with schizophrenia.
518 As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with
519 dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase

520 the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose
521 for any geriatric patient (*see* PRECAUTIONS and DOSAGE AND ADMINISTRATION).

522

ADVERSE REACTIONS

523

The information below is derived from a clinical trial database for olanzapine consisting of

524 4189 patients with approximately 2665 patient-years of exposure. This database includes:

525 (1) 2500 patients who participated in multiple-dose premarketing trials in schizophrenia and

526 Alzheimer's disease representing approximately 1122 patient-years of exposure as of

527 February 14, 1995; (2) 182 patients who participated in premarketing bipolar mania trials

528 representing approximately 66 patient-years of exposure; (3) 191 patients who participated in a

529 trial of patients having various psychiatric symptoms in association with Alzheimer's disease

530 representing approximately 29 patient-years of exposure; and (4) 1316 patients from 43 additional

531 clinical trials as of May 1, 1997. In addition, information from the premarketing 6-week clinical

532 study database for olanzapine in combination with lithium or valproate, consisting of 224 patients

533 who participated in bipolar mania trials with approximately 22 patient-years of exposure, is

534 included below.

535 The conditions and duration of treatment with olanzapine varied greatly and included (in

536 overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients,

537 fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions

538 were assessed by collecting adverse events, results of physical examinations, vital signs, weights,

539 laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

540 Certain portions of the discussion below relating to objective or numeric safety parameters,

541 namely, dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and

542 ECG changes are derived from studies in patients with schizophrenia and have not been duplicated

543 for bipolar mania. However, this information is also generally applicable to bipolar mania.

544 Adverse events during exposure were obtained by spontaneous report and recorded by clinical

545 investigators using terminology of their own choosing. Consequently, it is not possible to provide a

546 meaningful estimate of the proportion of individuals experiencing adverse events without first

547 grouping similar types of events into a smaller number of standardized event categories. In the

548 tables and tabulations that follow, standard COSTART dictionary terminology has been used

549 initially to classify reported adverse events.

550 The stated frequencies of adverse events represent the proportion of individuals who

551 experienced, at least once, a treatment-emergent adverse event of the type listed. An event was

552 considered treatment emergent if it occurred for the first time or worsened while receiving therapy

553 following baseline evaluation. The reported events do not include those event terms which were

554 so general as to be uninformative. Events listed elsewhere in labeling may not be repeated below.

555 It is important to emphasize that, although the events occurred during treatment with olanzapine,

556 they were not necessarily caused by it. The entire label should be read to gain a complete

557 understanding of the safety profile of olanzapine.

558 The prescriber should be aware that the figures in the tables and tabulations cannot be used to

559 predict the incidence of side effects in the course of usual medical practice where patient

560 characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the

561 cited frequencies cannot be compared with figures obtained from other clinical investigations

562 involving different treatments, uses, and investigators. The cited figures, however, do provide the

563 prescribing physician with some basis for estimating the relative contribution of drug and nondrug

564 factors to the adverse event incidence in the population studied.

565 **Incidence of Adverse Events in Short-Term, Placebo-Controlled and Combination**
 566 **Trials**

567 The following findings are based on premarketing trials for schizophrenia, bipolar mania, a
 568 subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's
 569 disease, and premarketing combination trials.

570 **Adverse Events Associated with Discontinuation of Treatment in Short-Term,**
 571 **Placebo-Controlled Trials**

572 Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to
 573 adverse events (5% for olanzapine vs 6% for placebo). However, discontinuations due to
 574 increases in SGPT were considered to be drug related (2% for olanzapine vs 0% for placebo)
 575 (see PRECAUTIONS).

576 Bipolar Mania Monotherapy — Overall, there was no difference in the incidence of
 577 discontinuation due to adverse events (2% for olanzapine vs 2% for placebo).

578 **Adverse Events Associated with Discontinuation of Treatment in Short-Term Combination**
 579 **Trials**

580 Bipolar Mania Combination Therapy — In a study of patients who were already tolerating either
 581 lithium or valproate as monotherapy, discontinuation rates due to adverse events were 11% for the
 582 combination of olanzapine with lithium or valproate compared to 2% for patients who remained on
 583 lithium or valproate monotherapy. Discontinuations with the combination of olanzapine and lithium
 584 or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and
 585 peripheral edema (1%).
 586

587 **Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials**

588 The most commonly observed adverse events associated with the use of olanzapine (incidence
 589 of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients
 590 (olanzapine incidence at least twice that for placebo) were:
 591

Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 6-Week Trials — SCHIZOPHRENIA		
Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder ¹	8	4
Akathisia	5	1

592 ¹ Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.
 593

Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 3-Week and 4-Week Trials — BIPOLAR MANIA		
Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=125)	Placebo (N=129)
Asthenia	15	6
Dry mouth	22	7
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

594

595 Adverse Events Occurring at an Incidence of 2% or More Among Olanzapine-Treated
596 Patients in Short-Term, Placebo-Controlled Trials

597 Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse
598 events that occurred in 2% or more of patients treated with olanzapine (doses ≥ 2.5 mg/day) and
599 with incidence greater than placebo who participated in the acute phase of placebo-controlled
600 trials.

601

Table 1
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials¹
Percentage of Patients Reporting Event

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=532)	Placebo (N=294)
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2
Hemic and Lymphatic System		

Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		
Extremity pain (other than joint)	5	3
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

602 ¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an
603 incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion,
604 depression, diarrhea, dysmenorrhea², hallucinations, headache, hostility, hyperkinesia, myalgia, nausea,
605 nervousness, paranoid reaction, personality disorder³, rash, thinking abnormal, weight loss.

606 ² Denominator used was for females only (olanzapine, N=201; placebo, N=114).

607 ³ Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

608

609 Commonly Observed Adverse Events in Short-Term Combination Trials

610 In the bipolar mania combination placebo-controlled trials, the most commonly observed
611 adverse events associated with the combination of olanzapine and lithium or valproate (incidence
612 of $\geq 5\%$ and at least twice placebo) were:

613

Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 6-Week Combination Trials — BIPOLAR MANIA		
Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Dry mouth	32	9
Weight gain	26	7

Increased appetite	24	8
Dizziness	14	7
Back pain	8	4
Constipation	8	4
Speech disorder	7	1
Increased salivation	6	2
Amnesia	5	2
Paresthesia	5	2

614

615 Adverse Events Occurring at an Incidence of 2% or More Among Olanzapine-Treated
616 Patients in Short-Term Combination Trials

617 Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse
618 events that occurred in 2% or more of patients treated with the combination of olanzapine (doses
619 ≥ 5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone
620 who participated in the acute phase of placebo-controlled combination trials.
621

Table 2
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Combination Clinical Trials¹

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Body as a Whole		
Asthenia	18	13
Back pain	8	4
Accidental injury	4	2
Chest pain	3	2
Cardiovascular System		
Hypertension	2	1
Digestive System		
Dry mouth	32	9
Increased appetite	24	8
Thirst	10	6
Constipation	8	4
Increased salivation	6	2
Metabolic and Nutritional Disorders		
Weight gain	26	7
Peripheral edema	6	4
Edema	2	1
Nervous System		
Somnolence	52	27
Tremor	23	13
Depression	18	17

Dizziness	14	7
Speech disorder	7	1
Amnesia	5	2
Paresthesia	5	2
Apathy	4	3
Confusion	4	1
Euphoria	3	2
Incoordination	2	0
Respiratory System		
Pharyngitis	4	1
Dyspnea	3	1
Skin and Appendages		
Sweating	3	1
Acne	2	0
Dry skin	2	0
Special Senses		
Amblyopia	9	5
Abnormal vision	2	0
Urogenital System		
Dysmenorrhea ²	2	0
Vaginitis ²	2	0

622 ¹ Events reported by at least 2% of patients treated with olanzapine, except the following events which had an
623 incidence equal to or less than placebo: abdominal pain, abnormal dreams, abnormal ejaculation, agitation,
624 akathisia, anorexia, anxiety, arthralgia, cough increased, diarrhea, dyspepsia, emotional lability, fever, flatulence,
625 flu syndrome, headache, hostility, insomnia, libido decreased, libido increased, menstrual disorder², myalgia,
626 nausea, nervousness, pain, paranoid reaction, personality disorder, rash, rhinitis, sleep disorder, thinking
627 abnormal, vomiting.

628 ² Denominator used was for females only (olanzapine, N=128; placebo, N=51).
629

630 For specific information about the adverse reactions observed with lithium or valproate, refer to
631 the ADVERSE REACTIONS section of the package inserts for these other products.

632 **Additional Findings Observed in Clinical Trials**

633 The following findings are based on clinical trials.

634 **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials**

635 Extrapyramidal Symptoms — The following table enumerates the percentage of patients with
636 treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating
637 scales during acute therapy in a controlled clinical trial comparing olanzapine at 3 fixed doses
638 with placebo in the treatment of schizophrenia.
639

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY RATING SCALES INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL — ACUTE PHASE*

	Percentage of Patients Reporting Event			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism ¹	15	14	12	14
Akathisia ²	23	16	19	27

640 * No statistically significant differences.

641 ¹ Percentage of patients with a Simpson-Angus Scale total score >3.

642 ² Percentage of patients with a Barnes Akathisia Scale global score ≥2.

643

644 The following table enumerates the percentage of patients with treatment-emergent
645 extrapyramidal symptoms as assessed by spontaneously reported adverse events during acute
646 therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in
647 the treatment of schizophrenia.

648

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY ADVERSE EVENTS INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL — ACUTE PHASE

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events ¹	1	3	2	3
Parkinsonism events ²	10	8	14	20
Akathisia events ³	1	5	11*	10*
Dyskinetic events ⁴	4	0	2	1
Residual events ⁵	1	2	5	1
Any extrapyramidal event	16	15	25	32*

649 * Statistically significantly different from placebo.

650 ¹ Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck
651 rigidity, oculogyric crisis, opisthotonos, torticollis.

652 ² Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity,
653 extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

654 ³ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

655 ⁴ Patients with the following COSTART terms were counted in this category: buccoglossal syndrome,
656 choreoathetosis, dyskinesia, tardive dyskinesia.

657 ⁵ Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus,
658 twitching.

659

660 Other Adverse Events — The following table addresses dose relatedness for other adverse
661 events using data from a schizophrenia trial involving fixed dosage ranges. It enumerates the
662 percentage of patients with treatment-emergent adverse events for the three fixed-dose range
663 groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the
664 placebo group, and the table includes only those adverse events for which there was a statistically
665 significant trend.

666

Adverse Event	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Asthenia	15	8	9	20
Dry mouth	4	3	5	13
Nausea	9	0	2	9
Somnolence	16	20	30	39
Tremor	3	0	5	7

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Vital Sign Changes — Olanzapine is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

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Weight Gain — In placebo-controlled, 6-week studies, weight gain was reported in 5.6% of olanzapine patients compared to 0.8% of placebo patients. Olanzapine patients gained an average of 2.8 kg, compared to an average 0.4 kg weight loss in placebo patients; 29% of olanzapine patients gained greater than 7% of their baseline weight, compared to 3% of placebo patients. A categorization of patients at baseline on the basis of body mass index (BMI) revealed a significantly greater effect in patients with low BMI compared to normal or overweight patients; nevertheless, weight gain was greater in all 3 olanzapine groups compared to the placebo group. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

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Laboratory Changes — An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (see PRECAUTIONS). Olanzapine administration was also associated with increases in serum prolactin (see PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

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Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models (see ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

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ECG Changes — Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine use was associated with a mean increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes (see PRECAUTIONS).

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Other Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with olanzapine (at multiple doses ≥ 1 mg/day) in clinical trials (4189 patients, 2665 patient-years of exposure). This listing does not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

704

705

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least

706 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials
707 appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients;
708 rare events are those occurring in fewer than 1/1000 patients.

709 **Body as a Whole** — *Frequent*: dental pain, flu syndrome, intentional injury, and suicide
710 attempt; *Infrequent*: abdomen enlarged, chills, chills and fever, face edema, malaise, moniliasis,
711 neck pain, neck rigidity, pelvic pain, and photosensitivity reaction; *Rare*: hangover effect and
712 sudden death.

713 **Cardiovascular System** — *Frequent*: hypotension; *Infrequent*: bradycardia, cerebrovascular
714 accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation,
715 vasodilatation, and ventricular extrasystoles; *Rare*: arteritis, atrial fibrillation, heart failure, and
716 pulmonary embolus.

717 **Digestive System** — *Frequent*: increased salivation and thirst; *Infrequent*: dysphagia,
718 eructation, fecal impaction, fecal incontinence, flatulence, gastritis, gastroenteritis, gingivitis,
719 hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess,
720 rectal hemorrhage, stomatitis, tongue edema, and tooth caries; *Rare*: aphthous stomatitis, enteritis,
721 esophageal ulcer, esophagitis, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue
722 discoloration.

723 **Endocrine System** — *Infrequent*: diabetes mellitus; *Rare*: diabetic acidosis and goiter.

724 **Hemic and Lymphatic System** — *Frequent*: leukopenia; *Infrequent*: anemia, cyanosis,
725 leukocytosis, lymphadenopathy, thrombocythemia, and thrombocytopenia; *Rare*: normocytic
726 anemia.

727 **Metabolic and Nutritional Disorders** — *Infrequent*: acidosis, alkaline phosphatase increased,
728 bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia,
729 hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema, and
730 water intoxication; *Rare*: gout, hyperkalemia, hypernatremia, hypoproteinemia, and ketosis.

731 **Musculoskeletal System** — *Frequent*: joint stiffness and twitching; *Infrequent*: arthritis,
732 arthrosis, bursitis, leg cramps, and myasthenia; *Rare*: bone pain, myopathy, osteoporosis, and
733 rheumatoid arthritis.

734 **Nervous System** — *Frequent*: abnormal dreams, emotional lability, euphoria, libido
735 decreased, paresthesia, and schizophrenic reaction; *Infrequent*: alcohol misuse, amnesia,
736 antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, coma, delirium, depersonalization,
737 dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido increased,
738 obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering,
739 tardive dyskinesia, tobacco misuse, vertigo, and withdrawal syndrome; *Rare*: akinesia, circumoral
740 paresthesia, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, and subarachnoid
741 hemorrhage.

742 **Respiratory System** — *Frequent*: dyspnea; *Infrequent*: apnea, aspiration pneumonia, asthma,
743 atelectasis, epistaxis, hemoptysis, hyperventilation, laryngitis, pneumonia, and voice alteration;
744 *Rare*: hiccup, hypoventilation, hypoxia, lung edema, and stridor.

745 **Skin and Appendages** — *Frequent*: sweating; *Infrequent*: alopecia, contact dermatitis, dry
746 skin, eczema, maculopapular rash, pruritus, seborrhea, skin ulcer, and vesicubullous rash;
747 *Rare*: hirsutism, pustular rash, skin discoloration, and urticaria.

748 **Special Senses** — *Frequent*: conjunctivitis; *Infrequent*: abnormality of accommodation,
749 blepharitis, cataract, corneal lesion, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye
750 inflammation, eye pain, ocular muscle abnormality, taste perversion, and tinnitus; *Rare*: glaucoma,
751 keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment deposits lens.

752 **Urogenital System** — *Frequent*: amenorrhea*, hematuria, metrorrhagia*, and vaginitis*;
753 *Infrequent*: abnormal ejaculation*, breast pain, cystitis, decreased menstruation*, dysuria, female
754 lactation, glycosuria, impotence*, increased menstruation*, menorrhagia*, polyuria, premenstrual

755 syndrome*, pyuria, urinary frequency, urinary retention, urination impaired, uterine fibroids
 756 enlarged*, and vaginal hemorrhage*; *Rare*: albuminuria, gynecomastia, mastitis, oliguria, and
 757 urinary urgency.

758 *Adjusted for gender.

759 **Postintroduction Reports**

760 Adverse events reported since market introduction which were temporally (but not necessarily
 761 causally) related to ZYPREXA therapy include the following: allergic reaction
 762 (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, pancreatitis, and
 763 priapism.

764 **DRUG ABUSE AND DEPENDENCE**

765 **Controlled Substance Class**

766 Olanzapine is not a controlled substance.

767 **Physical and Psychological Dependence**

768 In studies prospectively designed to assess abuse and dependence potential, olanzapine was
 769 shown to have acute depressive CNS effects but little or no potential of abuse or physical
 770 dependence in rats administered oral doses up to 15 times the maximum recommended human daily
 771 dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum
 772 recommended human daily dose on a mg/m² basis.

773 Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance,
 774 or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking
 775 behavior, these observations were not systematic, and it is not possible to predict on the basis of
 776 this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or
 777 abused once marketed. Consequently, patients should be evaluated carefully for a history of drug
 778 abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine
 779 (e.g., development of tolerance, increases in dose, drug-seeking behavior).

780 **OVERDOSAGE**

781 **Human Experience**

782 In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or
 783 intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the
 784 largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred
 785 speech. In the limited number of patients who were evaluated in hospitals, including the patient
 786 taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or
 787 ECG. Vital signs were usually within normal limits following overdoses.

788 During the first 2 years of marketing, Eli Lilly and Company received reports of 178 cases of
 789 possible or definite overdose with olanzapine alone (at doses up to 1500 mg). Symptoms possibly
 790 but not necessarily causally attributable to the overdose were reported in 76% of these cases
 791 while 24% of reported cases had no symptoms attributable to overdose. In symptomatic patients,
 792 symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia,
 793 various extrapyramidal symptoms, and reduced level of consciousness. Among less commonly
 794 reported symptoms were the following potentially medically serious events: aspiration,
 795 cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and one patient
 796 experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible
 797 neuroleptic malignant syndrome, coma, respiratory depression/arrest, convulsion, hypertension,
 798 and hypotension. Eli Lilly and Company has received reports of fatality in association with
 799 overdose of olanzapine alone. In one case of death, the amount of acutely ingested olanzapine was
 800 reported to be possibly as low as 450 mg; however, in another case, a patient was reported to
 801 survive an acute olanzapine ingestion of 1500 mg.

802 Overdosage Management

803 The possibility of multiple drug involvement should be considered. In case of acute overdosage,
804 establish and maintain an airway and ensure adequate oxygenation and ventilation, which may
805 include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of
806 activated charcoal together with a laxative should be considered. The possibility of obtundation,
807 seizures, or dystonic reaction of the head and neck following overdose may create a risk of
808 aspiration with induced emesis. Cardiovascular monitoring should commence immediately and
809 should include continuous electrocardiographic monitoring to detect possible arrhythmias.

810 There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should
811 be initiated. Hypotension and circulatory collapse should be treated with appropriate measures
812 such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or
813 other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension
814 in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring
815 should continue until the patient recovers.

816 DOSAGE AND ADMINISTRATION**817 Schizophrenia**

818 Usual Dose — Olanzapine should be administered on a once-a-day schedule without regard to
819 meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within
820 several days. Further dosage adjustments, if indicated, should generally occur at intervals of not
821 less than 1 week, since steady state for olanzapine would not be achieved for approximately
822 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements
823 of 5 mg QD are recommended.

824 Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials.
825 However, doses above 10 mg/day were not demonstrated to be more efficacious than the
826 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of
827 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above
828 20 mg/day has not been evaluated in clinical trials.

829 Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are
830 debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a
831 combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking
832 female patients ≥ 65 years of age), or who may be more pharmacodynamically sensitive to
833 olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant
834 Illness and Drug Interactions *under* PRECAUTIONS). When indicated, dose escalation should be
835 performed with caution in these patients.

836 Maintenance Treatment — While there is no body of evidence available to answer the question
837 of how long the patient treated with olanzapine should remain on it, the effectiveness of oral
838 olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients
839 who had been stable on ZYPREXA for approximately 8 weeks and were then followed for a
840 period of up to 8 months has been demonstrated in a placebo-controlled trial (*see* CLINICAL
841 PHARMACOLOGY). Patients should be periodically reassessed to determine the need for
842 maintenance treatment with appropriate dose.

843 Bipolar Mania

844 Usual Monotherapy Dose — Olanzapine should be administered on a once-a-day schedule
845 without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated,
846 should generally occur at intervals of not less than 24 hours, reflecting the procedures in the
847 placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of
848 5 mg QD are recommended.

849 Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to
850 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in
851 clinical trials.

852 Usual Dose in Combination with Lithium or Valproate — When administered in combination
853 with lithium or valproate, olanzapine dosing should generally begin with 10 mg once-a-day
854 without regard to meals.

855 Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day
856 in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

857 Dosing in Special Populations — See Dosing in Special Populations *under* DOSAGE AND
858 ADMINISTRATION, Schizophrenia.

859 Maintenance Treatment — There is no body of evidence available from controlled trials to
860 guide a clinician in the longer-term management of a patient who improves during treatment of an
861 acute manic episode with olanzapine. While it is generally agreed that pharmacological treatment
862 beyond an acute response in mania is desirable, both for maintenance of the initial response and
863 for prevention of new manic episodes, there are no systematically obtained data to support the use
864 of olanzapine in such longer-term treatment (i.e., beyond 6 weeks).

865 *Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)*

866 After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon
867 opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the
868 mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without
869 liquid.

870 HOW SUPPLIED

871 The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue
872 ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with
873 LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and
874 tablet number. The tablets are available as follows:

	TABLET STRENGTH					
	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg
Tablet No.	4112	4115	4116	4117	4415	4420
Identification	LILLY 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415	LILLY 4420
NDC Codes:						
Bottles 60	NDC 0002- 4112-60	NDC 0002- 4115-60	NDC 0002- 4116-60	NDC 0002- 4117-60	NDC 0002- 4415-60	NDC 0002- 4420-60
Blisters - ID* 100	NDC 0002- 4112-33	NDC 0002- 4115-33	NDC 0002- 4116-33	NDC 0002- 4117-33	NDC 0002- 4415-33	NDC 0002- 4420-33
Bottles 1000	NDC 0002- 4112-04	NDC 0002- 4115-04	NDC 0002- 4116-04	NDC 0002- 4117-04	NDC 0002- 4415-04	NDC 0002- 4420-04

876 * Identi-Dose® (unit dose medication, Lilly).

877

878 ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed
879 with the tablet strength. The tablets are available as follows:

880

ZYPREXA ZYDIS Tablets*	TABLET STRENGTH			
	5 mg	10 mg	15 mg	20 mg
Tablet No.	4453	4454	4455	4456
Debossed	5	10	15	20
NDC Codes:				
Dose Pack 30 (Child-Resistant)	NDC 0002- 4453-85	NDC 0002- 4454-85	NDC 0002- 4455-85	NDC 0002- 4456-85

881

882 ZYPREXA is a registered trademark of Eli Lilly and Company.

883 ZYDIS is a registered trademark of R. P. Scherer Corporation.

884 *ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and
885 Company by Scherer DDS Limited, United Kingdom, SN5 8RU.

886 Store at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. The USP defines
887 controlled room temperature as a temperature maintained thermostatically that encompasses the
888 usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean
889 kinetic temperature calculated to be not more than 25°C; and that allows for excursions between
890 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

891 Protect from light and moisture.

892

ANIMAL TOXICOLOGY

893 In animal studies with olanzapine, the principal hematologic findings were reversible peripheral
894 cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human
895 daily dose on a mg/m² basis), dose-related decreases in lymphocytes and neutrophils in mice, and
896 lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or
897 reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in
898 lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the
899 maximum recommended human daily dose on a mg/m² basis) in studies of 3 months' duration.
900 Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving
901 22.5 mg/kg (11 times the maximum recommended human daily dose on a mg/m² basis) for 3 months
902 or 16 mg/kg (8 times the maximum recommended human daily dose on a mg/m² basis) for 6 or
903 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined.
904 Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating
905 blood cells were probably due to peripheral (non-marrow) factors.

906 Literature revised Month dd, 2003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-018

MEDICAL REVIEW(S)

Clinical Review for NDA 20-592

NDA 20-592

Sponsor: Lilly

Drug: Zyprexa

Material Submitted: New Efficacy Supplement SE1-018

Date Submitted: 9/17/02

Date Received: 9/18/02

Medical Reviewer: Earl D. Hearst, MD

Date Completed: 5/21/03

Appears This Way
On Original

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Drug: Zyprexa 1

Material Submitted: New Efficacy Supplement SE1-018 1

Date Submitted: 9/17/02 1

Date Received: 9/18/02..... 1

Medical Reviewer: Earl D. Hearst, MD..... 1

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CLINICAL REVIEW

Executive Summary Section

Clinical Review for NDA 20-592

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Combination therapy adding olanzapine to lithium or valproate for the treatment of acute mania should be of benefit to clinicians. I recommend this submission be approved.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

□

□

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Two placebo-controlled studies supporting efficacy and safety were conducted under Protocol F1D-MC-HGFU ("Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder"). An additional study, F1D-LC-HGGB ("Divalproex Sodium/Valproic Acid Interaction Trial"), is also submitted.

B. Efficacy

The two part study HGFU provides evidence to support this submission for combination therapy adding olanzapine to lithium or valproate for the treatment of acute mania.

C. Safety

The studies HGFU and HGGB along with the lack of any significant adverse findings in the literature search and post marketing review provide reasonable evidence of safety for olanzapine used in combination therapy with lithium or valproate for the treatment of acute mania.

CLINICAL REVIEW

Executive Summary Section

D. Dosing

During HGFU Study Period II, patients received either olanzapine 5, 10, 15, or 20 mg/day or placebo. Dose- response was not evaluated within this range. The sponsor's directions for dosing are as follows:

“Usual Dose in Combination with Lithium or Valproate — When administered in combination with lithium or valproate, olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.”

E. Special Populations

Subgroup analyses were performed to examine the consistency of treatment effects over the strata of various demographic populations. The stratifying characteristics included in these analyses were age (<40 years, ≥40 years), gender, ethnic origin (Caucasian, other), mood stabilizer therapy (lithium or valproate), psychotic vs nonpsychotic features, bipolar mixed vs bipolar manic, presence or absence of a rapid cycling course, previous lithium exposure, previous valproate exposure, previous exposure to antipsychotic medications, and concomitant benzodiazepine use. A subgroup was analyzed only if the number of patients in each strata was 10 or more. For the primary efficacy variable Y-MRS total score, there were no statistically significant treatment-by-subgroup interactions.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

This submission studies olanzapine (Zyprexa) added to mood stabilizers in the treatment of bipolar disorder. The dose is from 5-20mg/day used in a population 18 to 69 years old.

B. State of Armamentarium for Indication(s)

Many other antipsychotics can be used in combination with a mood stabilizer for treatment of acute mania but I know of none currently approved for this use.

CLINICAL REVIEW

Clinical Review Section

C. Important Milestones in Product Development

SUMMARY OF PREVIOUS COMMUNICATIONS

February 20, 1997

A summary of the December 6, 1996 telephone conversation between Dr. Tom Laughren (FDA) and Dr. Gary Tollefson (Lilly) which focused on the clinical plan for registration of olanzapine monotherapy for the treatment of manic episodes associated with bipolar disorder was submitted to IND 28,705. A preliminary description of Protocol HGFU was part of that conversation.

May 15, 1997

A briefing document to support a pre-NDA meeting for the registration of olanzapine monotherapy for the treatment of manic or mixed episodes associated with bipolar disorder was submitted to IND 28,705. Protocol HGFU was summarized within this briefing document indicating that the study would start prior to submission of the supplemental NDA, but would not be part of the submission.

October 27, 1998

Protocol HGFU was summarized in a briefing document submitted to NDA 20-592 to support a meeting with the Division regarding further understanding of the FDA's position on issues described in the October 2, 1998 not approvable letter for NDA 20-592 S006 (olanzapine monotherapy for the treatment of manic or mixed episodes associated with bipolar disorder).

February 9, 2000

A briefing document summarizing Lilly's proposed bipolar disorder clinical plan, including the registration of the use of Zyprexa in combination with lithium or valproate, was submitted to IND 28,705 to support the February 23rd meeting.

February 23, 2000

A meeting was held between representatives of Lilly and the Agency to discuss Lilly's proposed bipolar disorder clinical plan, including the registration of the use of Zyprexa in combination with lithium or valproate. The Division indicated that achieving positive results in a single study evaluating the efficacy of olanzapine compared with placebo when each is added to lithium or valproate would be adequate for an adjunctive therapy acute mania claim.

March 16, 2000

Lilly's minutes of the February 23, 2000 meeting were submitted to IND 28,705.

May 14, 2002

A briefing document supporting the May 30, 2002 pre-NDA meeting was submitted to

CLINICAL REVIEW

Clinical Review Section

IND 28,705.

May 30, 2002

A pre-NDA meeting was held between representatives of Lilly and the Agency to discuss Lilly's planned supplemental NDA to support the approval of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes. The following agreements were reached during the meeting:

- 1) The Division agreed with the proposed content and format of the submission table of contents. Additionally, the Division agreed that an application summary, ISE, ISS and electronic Assay folder were not necessary.
- 2) The Division agreed that a study in pediatric patients evaluating olanzapine in combination with mood stabilizers in the treatment of bipolar mania would not be required and thus a pediatric waiver could be obtained.
- 3) The Division agreed that patient narratives should be provided for all patients who died, experienced a serious adverse event, discontinued due to adverse event, experienced other clinically significant adverse events defined as potentially clinically significant (PCS) low neutrophils, PCS low white blood counts, PCS QTc Bazett's formula and any other event determined by Lilly physician. The Division requested that the proposal to include patient narratives for patients who experience clinically significant adverse events defined as PCS high glucose abnormalities (> 250 mg/dL) should be changed to > 200 mg/dL. Additionally, the Division requested that patient narratives for patients who experience treatment-emergent diabetes where an oral antidiabetic agent or insulin is prescribed or patients who experience an exacerbation of diabetes where existing treatment with an oral antidiabetic agent is changed to insulin therapy be included in the submission.
- 4) The Division agreed that case report forms for patients who died, discontinued due to adverse events, and reported serious and unexpected adverse events should be included in the submission.
- 5) The Division agreed that the clinical pharmacology study HGGB does not meet the "covered study" definition for financial disclosure and thus only financial disclosure information from Protocol HGFU would be included in the submission.

June 10, 2002

Lilly's minutes of the May 30, 2002 meeting were submitted to IND 28,705.

June 21, 2002

Lilly received e-mail message from Mr. Randy Levin (FDA) confirming agreement with electronic format proposed in briefing document submitted May 14, 2002.

July 8, 2002

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Lilly received official minutes from FDA for the May 30, 2002 meeting.

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**List of INDs and NDAs
Olanzapine Applicable INDs**

IND Number	Initial Submission Date	Description
28,705	July 23, 1986	Olanzapine for the treatment of psychiatric disorders

Olanzapine Applicable NDAs

NDA Number	Initial Submission Date	Description
20-592	September 21, 1995	Olanzapine for the management of the manifestations of psychotic disorders
21-086	March 1, 1999	Olanzapine orally disintegrating tablets
21-253	June 15, 2000	Olanzapine for injection

D. Other Relevant Information

This combination indication is not approved in any other country.

E. Important Issues with Pharmacologically Related Agents

I have nothing to report in this section.

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II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Please see biopharm review and chemistry review.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The pharmacokinetic characteristics of olanzapine have been previously assessed in a variety of studies. Because patients on stable doses of divalproex were enrolled in this study, the study design did not permit a direct assessment of changes in olanzapine pharmacokinetics. The sponsor feels the data for valproic acid plasma concentrations show that over the dosage range of divalproex, the range of therapeutic concentrations for valproic acid were not influenced substantially by coadministration of olanzapine. The sponsor feels therefore, that olanzapine does not affect the pharmacokinetics of divalproex. A summary of the biopharm review written by Veneeta Tandon, Ph.D. is reproduced below.

"A drug interaction study was also conducted to assess the effect of olanzapine on steady state valproate levels (Protocol F1F-LC-HGGB: Olanzapine- Divalproex sodium interaction trial).

The results showed that in vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. The effect of valproate on olanzapine pharmacokinetics could not be determined robustly from this study.

The information on Lithium interaction with olanzapine has been taken from Study E001; submitted September 21, 1995 with NDA 20-592. The results indicated that there was no interaction between olanzapine and lithium."

B. Pharmacodynamics

The sponsor feels that the data from HGGB show that there is neither a pharmacokinetic nor a pharmacodynamic interaction between divalproex sodium and olanzapine. Please see biopharm review.

IV. Description of Clinical Data and Sources

A. Overall Data

Two placebo-controlled studies supporting efficacy and safety were conducted under Protocol F1D-MC-HGFU ("Olanzapine Added to Mood Stabilizers in the Treatment of

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Bipolar Disorder”). This protocol evaluated olanzapine added to lithium or valproate versus placebo added to lithium or valproate for the acute treatment of bipolar mania. In addition, an extension phase of the protocol evaluated the longer-term effects of olanzapine added to lithium or valproate versus placebo added to lithium or valproate in maintaining treatment response for up to 18 months in patients who had shown positive response to olanzapine in either of the acute studies. An additional study, F1D-LC-HGGB (“Divalproex Sodium/Valproic Acid Interaction Trial”), is also submitted. This was a clinical pharmacology study that evaluated pharmacokinetic and pharmacodynamic interactions between olanzapine and divalproex/valproic acid. A second pertinent clinical pharmacology study (E001), Pharmacokinetic Interaction Study between Olanzapine and Lithium, Given Orally, after Single and Repeated Administration of Olanzapine in Healthy Volunteers, is provided by cross-reference to NDA 20-592.

The efficacy and safety results from these two acute phase studies conducted under one protocol (F1D-MC-HGFU: Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder) are provided in a single acute phase clinical study report. Results from the 18-month extension phase of Protocol HGFU is provided in a separate clinical study report intended to provide additional patient safety data supporting the application.

The analyses evaluated 344 randomized patients, with 229 patients (119 in Study 1 and 110 in Study 2) treated with olanzapine added to current mood stabilizer (Olz+MS) and 115 patients (56 in Study 1 and 59 in Study 2) treated with placebo added to current mood stabilizer (Pla+MS), following a 2:1 randomization allocation. At enrollment, 226 patients were being treated with valproate as a mood stabilizer and 117 were undergoing treatment with lithium; 1 patient was categorized as unspecified due to use of both mood stabilizers during the acute phase.

B. Tables Listing the Clinical Trials

Table 1 summarizes two completed studies in which olanzapine was administered in combination with two commonly used mood stabilizers, lithium and valproate, to patients with bipolar I disorder. In all, 386 patients received combination therapy.

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Table 1. Olanzapine Clinical Studies in Combination Therapy Submission

Study	Status	Comparators	Sample Size/ Population	Length of Study	Efficacy Measures	Primary Aspect of Bipolar Disorder Under Investigation
HGFU	Completed	Placebo plus valproate or lithium	N = 344 bipolar I disorder, manic and mixed	6 weeks DB acute; 18 months DB extension for responders	1° acute phase: YMRS 1° extension phase: Time to syndromic relapse 2°: HAM-D-21, PANSS, CGI-BP Severity, DSM- IV Checklist	Acute bipolar mania (olanzapine plus lithium or valproate); Prevention of relapse, bipolar mania and depression (olanzapine plus lithium or valproate)
HGGB	Completed	Placebo co- administered with divalproex	N = 42 bipolar I disorder or schizoaffective disorder stabilized on divalproex for 2 months	4 weeks	Not applicable (clinical pharmacology study of interaction between olanzapine and divalproex)	Not applicable (clinical pharmacology study of interaction between olanzapine and divalproex)

Abbreviations: 1° - primary measurement; 2° - secondary measurement; CGI-BP Severity - Clinical Global Impressions—Bipolar Version Severity of Illness; DB - double-blind; DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HAM-D-21 - Hamilton Psychiatric Rating Scale for Depression—21 items; N - number of patients; PANSS - Positive and Negative Syndrome Scale; YMRS - Young Mania Rating Scale.

C. Postmarketing Experience

The collection of adverse events for the spontaneous safety database of olanzapine began on 27 September 1996. Eli Lilly and Company collects all reported spontaneous adverse events for patients treated with olanzapine in the [] safety database. [] began as the safety database on 5 March 1998 and replaced the [] was the initial safety database utilized by Eli Lilly and Company and began on 1 March 1983. All the olanzapine data collected in [] was transferred to the [] database. The adverse events found in the olanzapine spontaneous safety database are coded to terms from the Medical Dictionary for Regulatory Affairs (MedDRA). Spontaneous adverse events are defined as adverse events occurring with a marketed product in a therapeutic setting or from a source other than a clinical trial or post-marketing study.

Adverse Event Reports in Patients Concomitantly Treated with Mood Stabilizers

To assess whether spontaneous adverse event reports for olanzapine when used concomitantly with mood stabilizers contribute significantly to information regarding the safety of olanzapine that is new or inconsistent with information already known, the Eli Lilly and Company [] database was searched for spontaneous adverse event reports involving patients who were reportedly treated with olanzapine in conjunction with mood stabilizers.

Methods Used to Identify Patients Concomitantly Treated with Mood Stabilizers

The [] database was searched electronically for spontaneous event reports temporally associated with the use of olanzapine and mood stabilizers. Prior to initiating the search, a list of mood stabilizers was developed. By reviewing current therapy textbooks, journal articles, and

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consultation with psychiatrists, the following 9 mood stabilizers were identified: lithium, carbamazepine, valproic acid, gabapentin, felbamate, tiagabine, topiramate, lamotrigine, and oxcarbazepine. For lithium and valproic acid, all salt forms and derivatives (valproic acid, valproate semisodium, divalproex sodium, and valproate sodium) were utilized in the search.

Table 3 lists the 9 mood stabilizers and the number of case reports associated with each agent. When the individual mood stabilizers and their respective percentages are added, the total number of cases and percentage of cases will be greater than 3,626 and 100%, respectively.

Table 3. Frequency of the Mood Stabilizer as a Concomitant Within the 21,213 Olanzapine Case Reports in the Spontaneous Safety Database

Mood Stabilizer	Number of Cases	Percentage of Cases
Valproic acid derivatives	1,646	45.39%
Lithium salts	1,336	36.85%
Carbamazepine	682	18.81%
Gabapentin	296	8.16%
Topiramate	85	2.34%
Lamotrigine	73	2.01%
Oxcarbazepine	30	0.83%
Tiagabine	4	0.11%
Felbamate	2	0.06%
Total	3,626 unique cases	

The database search used the “concomitant drug” field to find the 9 chemical entities classified as mood stabilizers. Events that occurred at the time of concomitant mood stabilizer use were incorporated, along with events that were reported secondary to an event associated with a concomitant mood stabilizer. A mood stabilizer may have been discontinued after an initial event and subsequent events developed. All events were incorporated into the mood stabilizer group.

Assessment/Discussion of Adverse Event Reports

The patient receiving olanzapine with a concomitant mood stabilizer comprised 17.1% of all the cases in the olanzapine adverse event database. Therefore, the search methodology found 3,626 case reports of olanzapine used in conjunction with a mood stabilizer. Because cases were included if the “indication for use” entry in this field was blank or nonspecified, more reports in this review were found than in the “indication for use” review (3,626 versus 2,496) previously discussed.

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In addition to displaying the absolute number of cases and a reporting ratio for each event term, the corresponding number and reporting ratio for case reports in patients not receiving concomitant mood stabilizers in the olanzapine spontaneous safety database (17,587 cases) are displayed.

Table 2 (see appendix) lists the 54 MedDRA preferred terms that were reported at a rate within patients treated concomitantly with mood stabilizers greater than or equal to twice that reported in patients not treated concomitantly with mood stabilizers, where the number of cases among patients treated with concomitant mood stabilizer therapy was ≥ 6 .

I have reviewed this table and find it hard to conclude that there is any clear trend other than that olanzapine and mood stabilizer have a higher general rate of side effects than mood stabilizer used alone. The proportional reporting rates in this table are highest for Lab test abnormal 6.6, T wave inversion 6.33, cholelithiasis 4.25 and diabetic coma 4.0. Please see Table 2 in appendix.

D. Literature Review

The following information was used to complete the literature search for the bipolar mania submission. The literature search start date was 01 January 1995 and the stop date was 31 March 2002. The key words for the literature search were bipolar disorder and treatment with olanzapine or LY177053 and olanzapine in combination with lithium, valproate, valproic acid, divalproex, sodium valproate, or depakote. The databases used to search these criteria consisted of Medline, Derwent Drug File, SciSearch, Embase, PsycINFO, and Biosis.

The sponsor feels the search did not identify any additional prospective, randomized, controlled studies of olanzapine combined with mood stabilizers other than the published results of Study HGFU, the pivotal study in this supplemental NDA (Tohen 2002). Nevertheless, the literature search identified case reports (Haddad 1999, Novac 1998 and Weisler 1997) and 3 open label studies (McElroy 1998, Sharma 1999 and Vieta 2001) that provide supportive evidence of the benefits of olanzapine when combined with mood stabilizers. The sponsor states that adverse events reported in these publications were consistent with the known safety profile of olanzapine.

I agree with the sponsor's conclusions regarding the literature search.

V. Clinical Review Methods

A. How the Review was Conducted

Trial HGFU is reviewed in detail. Trial HGGB is summarized with the reader referred to the biopharm review.

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B. Overview of Materials Consulted in Review

This supplemental NDA is submitted in electronic format according to the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs," also referred to as the Electronic Submissions Guidance.

Case Report Tabulations are provided by electronic media only, and are not included in the paper review copy. The electronic version of the supplemental NDA contains datasets for Studies HGFU and HGGB. The format of the electronic datasets and accompanying documentation conform to the Guidance for Electronic Submissions.

Case Report Forms (CRFs) are provided by electronic media only. They contain scanned images of CRFs for all patients who died, discontinued due to adverse events, and reported serious and unexpected adverse events. The CRFs are submitted in the Adobe Portable Document Format as specified in the Electronic Submissions Guidance.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI agreed to inspect the following sites for protocol F1D-MC-HGFU (acute therapy):

Center 018 Logue (N=49)
Center 030 Weisler (N=45)

On Jan. 24th, 2003 a letter was sent to Dr. Logue indicating his data was acceptable.

Although some deficiencies were noted at Dr. Weisler's site, data from these sites appear acceptable for use in support of this NDA supplement according to FDA reviewer Ni A. Khin, M.D.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Ethical Review HGFU

Protocol F1D-MC-HGFU and Amendment (a) to the original protocol were reviewed by multiple ethical review boards. The sponsor provided a list of all ethical review boards consulted which I have reviewed.

Ethical Conduct of the Study

This protocol was conducted and informed consent was obtained according to the ethical

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principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for Good Clinical Practice, or the applicable laws and regulations of the country where the protocol was conducted, whichever provided the greater protection of the individual.

Ethics HGGB

Ethical Review Board(s)

The protocol, informed consent document, and any amendments were approved by the Ethical Review Boards. The sponsor provided a list of all ethical review boards consulted which I have reviewed.

Ethical Conduct of the Study

This study was conducted and informed consent was obtained according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practice, or the applicable laws and regulations of the country where the study was conducted, whichever provided the greater protection of the individual.

E. Evaluation of Financial Disclosure

The Division agreed that the clinical pharmacology study HGGB does not meet the "covered study" definition for financial disclosure and thus only financial disclosure information from Protocol HGFU would be included in the submission.

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Format of Financial Disclosure Information

The Financial Disclosure information is provided for Protocol FID-MC-HGFU in a table format listing the investigators (including sub-investigators) and status of disclosure. We have also defined the due diligence process used to obtain the information. Since this covered study did not require disclosure, FDA Form 3454 is presented prior to the table, certifying that each investigator had nothing to disclose or for whom disclosure was not obtained. In cases where disclosure information was not obtained, the reason for this is provided.

Due Diligence Process for Collection of Financial Disclosure Information

The current Lilly procedure for obtaining financial disclosure information is to send a cover letter and form to each investigator (including principal investigator, co-investigator, and sub-investigator) prior to the beginning of each site's participation in the study. Because Protocol HGFU was initiated prior to the effective date for the Financial Disclosure final rule and the first release of the Lilly global policy statement on collection of financial disclosure, the cover letters and forms were mailed to each investigator at the completion of the study. For those sites where financial disclosure information was not received, an additional letter and form were sent to each investigator. If this attempt at obtaining the financial disclosure information failed, a certified letter was sent and follow-up telephone calls were made to the sites. If the information could not be obtained following numerous requests, specific documentation was noted and filed appropriately in the study files.

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I have reviewed this disclosure and find it acceptable with no significant conflicts of interest.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The two part study HGFU provides evidence to support this application for combination therapy adding olanzapine to lithium or valproate for the treatment of acute mania.

B. General Approach to Review of the Efficacy of the Drug

There is only one study (2 parts) HGFU related to efficacy and this will be reviewed in detail. This study HGFU is bulky due to the fact that reports for study 1, study 2 and combined studies 1 & 2 are all included in full. I have selected the key sections for discussion in order to provide a relatively succinct review.

C. Detailed Review of Trials by Indication

HGFU

The efficacy of olanzapine in combination with either lithium or valproate for 6 weeks of double-blind therapy was studied in two placebo-controlled, multicenter trials (HGFU Study 1, HGFU Study 2). Patients who completed the acute phase of the HGFU protocol and were considered responders were rerandomized to a double-blind therapy phase for an additional

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18 months of therapy.

The primary objective of HGFU was to evaluate the efficacy of olanzapine compared with placebo when each is added to a patient's current mood stabilizer therapy after both acute and long-term therapy.

PATIENT POPULATION

The patient population was comprised of male and female patients, ages 18 to 65, who met diagnostic criteria for bipolar I disorder, manic or mixed, with or without psychotic features, according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Patient Version (SCID-P).

INVESTIGATORS

This multicenter protocol was conducted by 40 investigators, all physicians with a specialty in psychiatry, at 42 study sites within the United States and Canada. Submission appendix 16.1.3 contains information on the qualifications of these investigators and information on other key individuals at the study sites. I have reviewed this and find it acceptable.

STUDY PROCEDURES

Study Period I was the screening and washout period of the study. Study Period II was the 6-week, acute, double-blind therapy period of the study. Patients were assessed weekly from Visit 2 through Visit 8 (Table HGFU.9.3), Schedule of Events). During Study Period II, the dose of mood stabilizer should have remained within the therapeutic range. The therapeutic range for lithium was 0.6 mEq/l to 1.2 mEq/l, and 50 µg/mL to 125 µg/mL for valproate. The dose of mood stabilizer must have been within this therapeutic range, as measured by no later than Visit 1 for the patient to enter Study Period II. Should the mood stabilizer have deviated from this therapeutic range during Study Period II, the investigator adjusted the dose of mood stabilizer to reestablish blood levels that were within this therapeutic range. During Study Period II, the therapeutic range must have been re-established and documented by within 14 days or the patient was discontinued from the study. The patient was to remain on the same mood stabilizer throughout Study Periods I and II.

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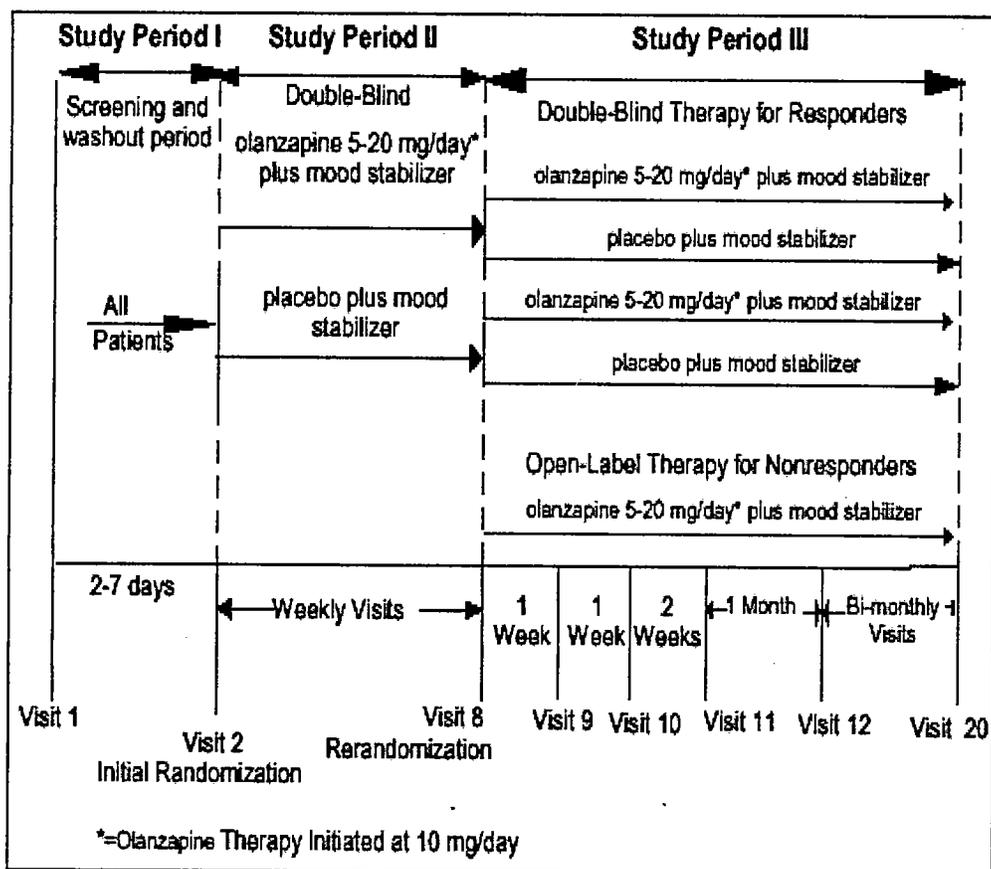


Figure HGFU.9.1. Illustration of Study Design F1D-MC-HGFU

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**Table HGFU.9.3. Schedule of Events
F1D-MC-HGFU**

Description of Data	V1	V2	V3-7	V8	V9	V10	V11	V12-19	V20	Final
Weeks until next visit	2-7 days	1	1	1	1	2	4	8		
Informed consent	X									
Demographics	X									
Kit number assigned		X		X						
Study drug compliance			X	X	X	X	X	X	X	
Height	X									
Weight and temperature	X	X	X	X	X	X	X	X	X	
Blood pressure and heart rate	X	X	X	X	X	X	X	X	X	
Psychiatric examination	X									
SCID-P	X									
Physical examination	X			X ^a						X
Electrocardiography	X			X ^a						X
Preexisting conditions and adverse events	X	X	X	X	X	X	X	X	X	
Historical illnesses and previous medications	X									
Study drug dispensed		X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	
Assessment of inpatient hospitalization	X	X	X	X	X	X	X	X	X	
Visit comments	X	X	X	X	X	X	X	X	X	
Adverse event follow-up										X
Patient summary including comments				X						X
LABORATORY TESTS										
Clinical chemistry ^b	X	X	X	X	X	X	X	X	X	X
Electrolyte group	X	X		X						X
Hematology	X	X		X						X
Urinalysis	X									X
TSH	X									
Hepatitis screen ^c , urine drug screen, and pregnancy test ^d	X									
Prolactin Levels		X		X						X
Serum concentration of lithium or valproate ^e	X	X	X	X	X	X	X	X	X	
EFFICACY MEASURES										
Y-MRS	X	X	X	X	X	X	X	X	X	
PANSS	X	X	X	X	X	X	X	X	X	
HAMD-21	X	X	X	X	X	X	X	X	X	
CGI-BP	X	X	X	X	X	X	X	X	X	
QUALITY OF LIFE MEASURES										
Lehman Brief Quality of Life Interview		X		X				X	X	
Resource Utilization		X		X				X	X	

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**Table HGFU.9.3. Schedule of Events
F1D-MC-HGFU (concluded)**

Description of Data	V1	V2	V3-7	V8	V9	V10	V11	V12-19	Visit 20	Final
SAFETY MEASURES										
Simpson-Angus Scale	X	X	X	X	X	X	X	X	X	
Barnes Akathisia Scale	X	X	X	X	X	X	X	X	X	
AIMS	X	X	X	X	X	X	X	X	X	
AMDP-5		X	X	X	X	X	X	X	X	

Abbreviations: V=visit; SCID-P=Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Patient Version; TSH=thyroid stimulating hormone; Y-MRS=Young-
Mania Rating Scale; PANSS=Positive and Negative Symptom Scale; HAMD-21=Hamilton Psychiatric
Rating Scale for Depression-21 Items; CGI-BP=Clinical Global Impression-Bipolar Version;
AIMS=Abnormal Involuntary Movement Scale; AMDP-5=Association for Methodology and
Documentation in Psychiatry Rating Scale.

- a The electrocardiogram and Physical Exam should were only to be performed at Visit 8 if the patient was discontinuing the study.
- b For Visits 3 through 7 and 9 through 19, unless clinically indicated by the physician, only the following laboratory tests were performed: aspartate transaminase (AST/SGOT), alanine transaminase (ALT/SGPT), total bilirubin, alkaline phosphatase, and gamma-glutamyl transferase (GGT).
- c Any patient who showed an increase from baseline (Visit 2) in AST/SGOT, ALT/SGPT, GGT, total bilirubin, or alkaline phosphatase to ≥ 3 times the upper limit of the laboratory reference range may have had the following tests performed: anti-HAV(IgM), HBsAg, and anti-HCVab.
- d Serum pregnancy test was performed on all females at Visit 1 and when clinically indicated.
- e It was strongly encouraged that the mood stabilizer level be assessed at the trough. Trough level was defined as within 2 hours prior to the next scheduled dose of mood stabilizer.

PRIMARY EFFICACY ANALYSIS

For the acute (6-week) phase of HGFU, the primary efficacy analysis was baseline to endpoint (LOCF) change in the Young Mania Rating Scale (YMRS) total score. Secondary assessments included change from baseline to endpoint in the YMRS, Positive and Negative Symptom Scale (PANSS) (total, positive, and negative), the Hamilton Psychiatric Rating Scale for Depression—21 Items (HAMD-21), and the Clinical Global Impressions—Bipolar Version Severity of Illness (CGI-BP Severity).

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Demographic Characteristics

For study 1 demographic characteristics are summarized in (Table HGFU.11.1). Patients had a mean age of 39.8 years; 82.9% were Caucasian; and 40.6% were male. The treatment groups were comparable at baseline with respect to mean age, ethnic origin and gender.

**Table HGFU.11.1. Demographic Characteristics
F1D-MC-HGFU Study 1**

Variable	Placebo (N=56)	Ols (N=119)	Total (N=175)	p-Value
Sex: No. (%)				
No. Patients	56	119	175	.099*
Male	28 (50.0)	43 (36.1)	71 (40.6)	
Female	28 (50.0)	76 (63.9)	104 (59.4)	
Origin: No. (%)				
No. Patients	56	119	175	.618*
Caucasian	47 (83.9)	98 (82.4)	145 (82.9)	
African Descent	5 (8.9)	15 (12.6)	20 (11.4)	
East/SE Asian	0	2 (1.7)	2 (1.1)	
Western Asian	1 (1.8)	1 (0.8)	2 (1.1)	
Hispanic	2 (3.6)	1 (0.8)	3 (1.7)	
Other Origin	1 (1.8)	2 (1.7)	3 (1.7)	
Age: yrs.				
No. Patients	56	119	175	.750**
Mean	40.26	39.63	39.84	
Median	39.49	39.93	39.81	
Standard Dev.	10.62	10.91	10.79	
Minimum	19.88	18.89	18.89	
Maximum	69.59	67.92	69.59	

The following Investigators were pooled : (011 028 034 036 041 043)

RMP.FIDP.JCLLIE (ASBSAFU)

RMP.FIDP.SASMACRO (SBASRA)

* Frequencies are analyzed using a Fishers-Exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance

(ANOVA); PROC GLM model=investigator, treatment, and interaction.

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For study 2, demographic characteristics are summarized in (Table HGFU.11.51). Patients had a mean age of 41.4 years; 87.6% were Caucasian; and 55.6% were male. The treatment groups were comparable at baseline with respect to mean age, ethnic origin, and gender.

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**Table HGFU.11.51. Demographic Characteristics
F1D-MC-HGFU Study 2**

Variable	Placebo (N=59)	Olz (N=110)	Total (N=169)	p-Value
Sex: No. (%)				
No. Patients	59	110	169	.333*
Male	36 (61.0)	58 (52.7)	94 (55.6)	
Female	23 (39.0)	52 (47.3)	75 (44.4)	
Origin: No. (%)				
No. Patients	59	110	169	.737*
Caucasian	50 (84.7)	98 (89.1)	148 (87.6)	
African Descent	5 (8.5)	7 (6.4)	12 (7.1)	
Hispanic	4 (6.8)	4 (3.6)	8 (4.7)	
Other Origin	0	1 (0.9)	1 (0.6)	
Age: yrs.				
No. Patients	59	110	169	.890**
Mean	40.57	41.91	41.44	
Median	38.61	42.32	40.54	
Standard Dev.	11.09	11.52	11.36	
Minimum	20.59	18.04	18.04	
Maximum	68.02	69.02	69.02	

The following Investigators were pooled : (005 008 020 035 039)

RMP.F1DP.JCLLIB(ASBSAFU)

RMP.F1DP.SASHMACRO(SEASEA)

* Frequencies are analyzed using a Fishers-Exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA); PROC GLM model=investigator, treatment, and interaction.

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ILLNESS CHARACTERISTICS

In this study, 48.0% of the patients were bipolar manic and 52.0% were bipolar mixed. Overall, 45.1% of the patients had a rapid cycling course, and 33.1% were exhibiting psychotic features in their current episode of mania. The treatment groups were comparable at baseline in that there were no statistically significant differences between treatment groups in these illness characteristics.

DISPOSITION OF THE RANDOMIZED PATIENTS

Table HGFU.10.2 summarizes the disposition of the randomized patients and the reasons the patients discontinued from the acute phase of the study. There was no statistically significant difference in the proportion of patients who completed the acute phase of the study between the Olz+MS (73.1%) and Pla+MS (76.8%) treatment groups. In order to be considered "reporting interval complete", patients must have completed Visit 8 and

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not have discontinued because of an adverse event. However, the proportion of patients who discontinued from the acute phase of the study due to lack of efficacy was statistically significantly different ($p=.035$) between the Olz+MS treatment group (1.7%) and the Pla+MS treatment group (8.9%).

**Table HGFU.10.2. Patient Disposition
F1D-MC-HGFU Study 1**

Reason for Discontinuation	Placebo (N=98) n (%)	Olz (N=119) n (%)	Total (N=178) n (%)	p-Value*
Reporting Interval Complete	63 (74.6)	87 (73.1)	150 (74.9)	.712
Adverse Event	2 (3.6)	11 (9.3)	13 (7.4)	.229
Lack of Efficacy	5 (8.6)	3 (3.9)	8 (4.6)	.035
Lost to Follow-up	1 (2.0)	4 (3.4)	5 (2.9)	1.00
Patient Decision	1 (2.0)	4 (3.4)	5 (2.9)	1.00
Criteria not met / Compliance	2 (3.6)	10 (8.4)	12 (6.8)	.362
Physician Decision	2 (3.6)	1 (0.8)	3 (1.7)	.268

IMP: F1DP, JULLIB (ASPTDAPU)
 IMP: F1DP, GRPMACRO (SPRTRDA)
 * Proportions are analyzed using a Fisher's Exact test.
 KR100901

Category (VITANK) F1D-MC-HGFU

**Table HGFU.10.3. Patient Disposition by Week
F1D-MC-HGFU Study 1**

Reason for Discontinuation	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Reporting Interval Complete	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	63 (74.6)
Adverse Event	0 (0)	0 (0)	1 (2.0)	0 (0)	1 (2.0)	0 (0)
Lack of Efficacy	1 (2.0)	0 (0)	1 (2.0)	1 (2.0)	2 (4.0)	0 (0)
Lost to Follow-up	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)
Patient Decision	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)	0 (0)
Criteria not met / Compliance	0 (0)	0 (0)	1 (2.0)	1 (2.0)	0 (0)	0 (0)
Physician Decision	1 (2.0)	1 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient discontinuing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	0 (0)	0 (0)	2 (4.0)	1 (2.0)	3 (6.0)	63 (74.6)

IMP: F1DP, JULLIB (ASPTDAPU)
 IMP: F1DP, GRPMACRO (SPRTRDA)
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Cartagena 5113025 F1D-MC-HGFU

**Table HGFU.10.3. Patient Disposition by Visit
F1D-MC-HGFU Study 1 (concluded)**

Treatment Group: Ols
Number of patients in the therapy group: 10113

Reason for Discontinuation	Visit 2		Visit 4		Visit 6		Visit 8		Visit 10	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Reporting Interval Complete	0	0	0	0	0	0	0	0	0	0 (0.0)
Adverse Event	0 (0.0)	4 (4.0)	3 (3.0)	0	0	0	0	0	0	0 (0.0)
Lack of Efficacy	1 (0.0)	0	1 (0.0)	0	0	0	0	0	0	0
Lost to Follow-up	1 (0.0)	1 (1.0)	1 (0.0)	0	0	0	0	0	0	0
Patient Decision	1 (0.0)	0	0	0	0	0	0	0	0	0
Criteria not met / Compliance	2 (2.0)	0	2 (2.0)	0	0	0	0	0	0	0
Physician Decision	0	0	0	0	0	0	0	0	0	0
Total	11 (1.0)	14 (1.4)	14 (1.4)	0						

IMP: F1D9 .JULIEN (MPTDAPF)
IMP: F1D9 .SARINACRO (MPTDAPF)
ENDPAGE

Table HGFU.10.7 summarizes the disposition of the randomized patients and the reasons the patients discontinued from the acute phase of the study. There was no statistically significant difference in the proportion of patients who completed the acute phase of the study between the Olz+MS (66.4%) and the Pla+MS (66.1%) treatment groups. In order to be considered "reporting interval complete", patients must have completed Visit 8 and not have discontinued because of an adverse event. There was, however, a statistically significantly greater proportion ($p=.021$) of patients who discontinued the acute phase of the study due to lack of efficacy in the Pla+MS treatment group (15.3%) than in the Olz+MS treatment group (4.5%). In addition, there was a statistically significantly greater proportion ($p=.002$) in the Olz+MS treatment group (12.7%) who discontinued due to adverse events than in the Pla+MS treatment group (0%).

**Table HGFU.10.7. Patient Disposition
F1D-MC-HGFU Study 2**

Reason for Discontinuation	Placebo (N=59)		Ols (N=110)		Total (N=169)	p-Value*
	n (%)	n (%)	n (%)	n (%)		
Reporting Interval Complete	39 (66.1)	73 (66.4)	112 (66.3)	1.00		
Satisfactory Response	0	1 (0.9)	1 (0.6)	1.00		
Adverse Event	0	14 (12.7)	14 (8.3)	.002		
Lack of Efficacy	0 (0.0)	5 (4.5)	5 (3.0)	.021		
Lost to Follow-up	2 (3.4)	1 (0.9)	3 (1.8)	.379		
Patient Decision	1 (1.7)	0 (0.0)	1 (0.6)	.168		
Criteria not met / Compliance	1 (1.7)	2 (1.8)	3 (1.8)	.344		
Physician Decision	1 (1.7)	1 (0.9)	2 (1.2)	1.00		
Physician Decision	4 (6.8)	4 (3.6)	8 (4.7)	.052		

IMP: F1D9 .JULIEN (MPTDAPF)
IMP: F1D9 .SARINACRO (MPTDAPF)
* Frequencies are analyzed using a Fisher's Exact test.
ENDPAGE

Table HGFU. 10.8 lists the number and percentage of patients in each treatment group who discontinued from the acute phase at each visit and the reason for discontinuation.

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**Table HGFL98.B. Patient Disposition by Visit
F10-MC-HGFU Study 2**

Evolutional Group: Fluoxetine
Number of patients in the therapy group: 66-551

	Visit 2	Visit 4	Visit 6	Visit 8	Visit 9	Visit 8
	n (%)	n (%)				
Reason for Discontinuation						
Reporting adverse symptoms	0	0	0	0	0	20 (36.4)
Lack of efficacy	0	3 (5.3)	3 (5.4)	3 (5.3)	3 (5.4)	0
Lost to follow-up	0	0	3 (5.4)	0	3 (5.4)	0
Patient dropped	0	0	3 (5.4)	0	0	0
Adverse not met / Compliance	3 (5.4)	3 (5.4)	0	0	3 (5.4)	0
Spontaneous resolution	3 (5.4)	0	0	0	3 (5.4)	0
Physician decision	3 (5.4)	3 (5.4)	0	0	3 (5.4)	0
Patients continuing	54 (84.6)	51 (84.6)	47 (79.7)	45 (74.3)	39 (64.0)	0

MSD / P100 / P11111 / CAPTIVE
MSD / P100 / P11111 / CAPTIVE
KIND0002

continued

**Table HGFL98.B. Patient Disposition by Visit
F10-MC-HGFU Study 2 (continued)**

Evolutional Group: Citalopram
Number of patients in the therapy group: 48-2107

	Visit 2	Visit 4	Visit 6	Visit 8	Visit 9	Visit 8
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Reason for Discontinuation						
Reporting adverse symptoms	0	0	0	0	0	20 (41.7)
Satisfactory Response	0	0	3 (6.3)	0	0	0
Adverse events	0 (0.0)	4 (8.3)	3 (6.3)	1 (2.1)	0	3 (6.3)
Lack of efficacy	0 (0.0)	0	3 (6.3)	0	3 (6.3)	3
Lost to follow-up	0	0	3 (6.3)	0	0	0
Physician Decision	3 (6.3)	3 (6.3)	3 (6.3)	0	3 (6.3)	0
Adverse not met / Compliance	0	3 (6.3)	0	0	3 (6.3)	0
Spontaneous resolution	0 (0.0)	0	0	0	0	0
Physician decision	0 (0.0)	3 (6.3)	3 (6.3)	0	3 (6.3)	0
Patients continuing	48 (100.0)	44 (91.7)	45 (93.8)	41 (85.4)	36 (75.0)	0

MSD / P100 / P11111 / CAPTIVE
MSD / P100 / P11111 / CAPTIVE
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Concomitant Medications

Patients took a variety of concomitant medications. There were no statistically significant differences between treatment groups in the use of any concomitant medications during the study.

Baseline Efficacy Scores

Results of treatment-group comparisons at baseline for both the primary (Y-MRS total score) and secondary (PANSS total, positive, and negative scores; HAMD-21 total score; and CGI-BP Severity scores) efficacy parameters, along with their respective descriptive

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statistics, are presented . There was no evidence of any statistically significant treatment-group differences at baseline.

RESULTS

Patients were randomized to one of 2 treatment groups: olanzapine in a flexible dose range of 5 to 20 mg/day added to current mood stabilizer therapy (Olz+MS), or placebo added to current mood stabilizer therapy (Pla+MS).

In both trials, the Olz+MS treatment group showed a greater level of improvement in YMRS total score than the Pla+MS treatment group. In HGFU Study 1, this improvement was -13.22 compared to -9.20 ($p=.051$), and for HGFU Study 2, this improvement was -12.99 compared to -9.00 ($p=.025$).

In both studies, mean reductions in the Hamilton Psychiatric Rating Scale for Depression—21 Items (HAM-D-21) total and the Clinical Global Impressions—Bipolar Version Severity of Illness (CGI-BP Severity) of depression scores were statistically significant for the Olz+MS treatment group compared with the Pla+MS treatment group. In both studies, the Positive and Negative Syndrome Scale (PANSS) total score showed a statistically significantly greater mean reduction in the Olz+MS treatment group compared with the Pla+MS treatment group.

Response rate (defined as a decrease of 50% or more in the YMRS total score) of the Olz+MS treatment group was nearly 1.5 times greater than that of the Pla+MS treatment group (69.0% versus 46.4%) in HGFU Study 1, and over 1.5 times greater (66.3% versus 43.1%) in HGFU Study 2. The treatment group difference was statistically significant in favor of Olz+MS in both studies.

The following tables show that study one is generally positive even though the primary efficacy variable just misses at $p=.051$. Study two and the combined studies are positive throughout for the primary efficacy variable (YMRS change from baseline) and most secondary variables.

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**Table HGFU.11.1B. Efficacy Scores
Mean Change From Baseline to Endpoint
F1D-MC-HGFU Study 1**

Variables Analyzed	Therapy	n	Baseline		Change to Endpoint		p-Value
			Mean	SD	Mean	SD	
CS_DEPR	Placebo	56	3.82	1.33	-0.84	1.23	.010
	Olz	116	3.84	1.49	-0.82	1.20	(.974)
CS_MANIA	Placebo	56	3.95	0.99	-0.93	1.22	.061
	Olz	116	3.69	0.98	-1.01	1.20	(.309)
CS_OVER	Placebo	56	4.09	0.64	-0.78	1.11	.011
	Olz	116	4.88	0.90	-1.16	1.13	(.477)
HAM-D-21	Placebo	56	18.83	7.01	-3.86	7.21	.006
	Olz	116	16.10	8.90	-4.82	7.01	(.923)
PAN-NEG	Placebo	56	13.61	4.71	-1.11	4.76	.119
	Olz	116	13.39	4.93	-1.91	4.34	(.685)
PAN-POS	Placebo	56	14.21	6.21	-3.88	8.04	.003
	Olz	116	14.21	4.93	-4.93	8.04	(.623)
PAN-TOT	Placebo	56	27.82	15.81	-8.86	16.87	.006
	Olz	116	24.39	17.91	-14.51	16.13	(.689)
YMRS-TOT	Placebo	56	21.87	3.82	-3.28	8.28	.061
	Olz	116	21.73	5.77	-13.22	8.23	(.620)

The following Investigators were pooled: (011 016 016 016 041 043)

IMP: F1D, JULLEN (AFFP/00V)

IMP: F1D, SANDRACHO (SAP/00L)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL2 - *1 Type III Sum of Squares from an analysis of variance (ANOVA); PROC GLM model; treatment, and interaction.

Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

ELAS0001

Legend of Variable Abbreviations:

Abbrev.	Description
CS_DEPR	CGI-RP Severity of Depression
CS_MANIA	CGI-RP Severity of Mania
CS_OVER	CGI-RP Sev. of Overall Bipolar Illness
HAM-D-21	HAM-D-21 Total Score
PAN-NEG	PANIS Negative Score
PAN-POS	PANIS Positive Score
PAN-TOT	PANIS Total Score
YMRS-TOT	YMRS Total Score

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**Table HGFU.11.29. Y-MRS Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGFU Study 1**

Visit	Week	Placebo (1)		OLA (2)	
		n	Mean SD	n	Mean SD
3	1	54	-4.23 8.28	114	-7.45 8.43
4	2	54	-7.46 7.93	114	-10.22 7.62
5	3	54	-7.18 8.98	114	-10.47 7.79
6	4	54	-8.78 7.93	114	-11.68 8.28
7	5	54	-10.43 8.34	114	-12.52 8.41
8	6	54	-9.28 8.28	114	-11.33 8.35

-----p-Values-----

Visit	Week	Overall	Inter- action
3	1	.034	.043
4	2	.184	.281
5	3	.091	.229
6	4	.026	.439
7	5	.161	.443
8	6	.051	.479

The following investigators were pooled : (011 028 034 036 041 043)
 HSP.F1DP.ACCLIN(ASHPALFU)
 HSP.F1DP.SANMACHO(SHPCTB)

*1 Type III Sum of Squares from an analysis of variance (ANOVA);
 PROC GLM model-investigator, treatment and interaction for the interaction and overall
 p-Value.

**Table HGFU.11.30. HAMD-21 Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGFU Study 1**

Visit	Week	Placebo (1)		OLA (2)	
		n	Mean SD	n	Mean SD
3	1	54	-1.84 4.53	114	-4.43 5.77
4	2	54	-2.95 4.52	114	-6.42 4.84
5	3	54	-3.14 4.44	114	-6.48 4.18
6	4	54	-3.37 4.41	114	-9.95 7.24
7	5	54	-3.19 4.79	114	-8.48 4.97
8	6	54	-2.95 7.21	114	-6.92 7.91

-----p-Values-----

Visit	Week	Overall	Inter- action
3	1	.051	.231
4	2	.079	.268
5	3	.408	.248
6	4	.191	.181
7	5	.123	.498
8	6	.001	.031

The following investigators were pooled : (011 028 034 036 041 043)
 HSP.F1DP.ACCLIN(ASHPALFU)
 HSP.F1DP.SANMACHO(SHPCTB)

*1 Type III Sum of Squares from an analysis of variance (ANOVA);
 PROC GLM model-investigator, treatment and interaction for the interaction and overall
 p-Value.

APPENDIX 11.30
 HAMD-21

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Table HGFU.11.69. Efficacy Scores
Mean Change from Baseline to Endpoint
F1D-MC-HGFU Study 2

Research Project Code: F1D

Variables Analyzed	Therapy	n	Change to				p-Values
			Baseline	SD	Endpoint	SD	
			Mean		Mean	SD	Therapy (Int'l)
CF_DEPR	Placebo	51	2.24	1.32	0.28	1.59	.614
	Olz	104	2.04	1.29	-0.77	1.44	(.423)
CF_MANIA	Placebo	51	4.31	0.75	-1.38	1.52	.218
	Olz	104	4.14	0.63	-1.57	1.34	(.484)
CF_OVER	Placebo	51	0.32	0.78	-1.07	1.04	.344
	Olz	104	4.13	0.52	-1.14	1.30	(.611)
HAMM170	Placebo	51	11.34	7.62	0.34	4.45	.803
	Olz	104	12.66	7.56	-1.83	8.10	(.653)
FAMNSMG	Placebo	51	10.26	1.57	-0.12	3.56	.323
	Olz	104	11.37	3.11	-1.18	4.85	(.747)
FAMNSPF	Placebo	51	15.97	2.49	-1.13	5.13	.462
	Olz	104	19.02	4.70	-0.99	4.61	(.874)
FAMNSTOT	Placebo	51	54.44	11.40	-1.60	13.04	.028
	Olz	104	58.44	15.81	-11.12	15.04	(.221)
YERSTOT	Placebo	51	12.24	4.10	-9.80	3.51	.825
	Olz	104	12.39	4.97	-12.29	8.89	(.404)

The following investigators were pooled: (001 001 002 003 004)

IMP.F1DP.NCLL13(AMF1M7U)

IMP.F1DP.SAMACHO(AMAPR11)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL3 - *1 Type III Sums of Squares from an analysis of variance (ANOVA); PROC GLM model; cov., treatment, and interaction.

Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

ELASFORM

Legend of Variable Abbreviations:

Abbrev.	Description
CF_DEPR	CGI-SF Severity of Depression
CF_MANIA	CGI-SF Severity of Mania
CF_OVER	CGI-SF Sev. of Overall Bipolar Illness
HAMM170	HAMD-21 Total Score
FAMNSMG	FAMS Negative Score
FAMNSPF	FAMS Positive Score
FAMNSTOT	FAMS Total Score
YERSTOT	YRS Total Score

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**Table HGFU.11.79. Y-MRS Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGFU Study 2**

Visit	Week	Placebo (1)		Ols (2)	
		n	Mean SD	n	Mean SD
3	1	54	-5.47 4.83	104	-5.50 4.50
4	2	54	-7.47 7.38	104	-7.21 7.39
5	3	54	-8.79 7.76	104	-9.49 8.16
6	4	54	-9.43 8.19	104	-9.61 8.95
7	5	54	-9.97 9.38	104	-12.04 8.84
8	6	54	-9.49 9.51	104	-12.99 8.68

-----p-Values*1-----

Visit	Week	Overall	Inter- action
3	1	.466	.463
4	2	.531	.461
5	3	.498	.412
6	4	.487	.401
7	5	.497	.374
8	6	.434	.404

The following investigators were pooled : (001 001 001 001 001)
IMP.F1DP.JCLL1B (ASFP1LPU)
IMP.F1DP.SAMM1C0 (SEPC1B)

*1 Type III Sum of Squares from an analysis of variance (ANOVA);
PROC GLM model=investigator, treatment and interaction for the interaction and overall
p-Value.

**Table HGFU.11.80. HAMD-21 Total Score
Visitwise Change from Baseline (LOCF)
F1D-MC-HGFU Study 2**

Visit	Week	Placebo (1)		Ols (2)	
		n	Mean SD	n	Mean SD
3	1	54	9.34 5.29	104	9.02 5.19
4	2	54	8.85 5.45	104	8.19 5.83
5	3	54	8.33 4.49	104	8.39 5.76
6	4	54	8.14 4.42	104	8.06 4.38
7	5	54	8.53 5.86	104	8.74 4.76
8	6	54	8.34 6.48	104	8.01 4.19

-----p-Values*1-----

Visit	Week	Overall	Inter- action
3	1	.401	.384
4	2	.401	.424
5	3	.401	.571
6	4	.412	.462
7	5	.462	.433
8	6	.462	.453

The following investigators were pooled : (001 001 001 001 001)
IMP.F1DP.JCLL1B (ASFP1LPU)
IMP.F1DP.SAMM1C0 (SEPC1B)

*1 Type III Sum of Squares from an analysis of variance (ANOVA);
PROC GLM model=investigator, treatment and interaction for the interaction and overall
p-Value.

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Table HQFU.11.119. Efficacy Scores
Mean Change from Baseline to Endpoint
F1D-MC-HGFU Studies 1 and 2 Combined

Research Project Code: F1D

Variables Analyzed	Therapy	n	Baseline		Change to Endpoint		p-Value
			Mean	SD	Mean	SD	
CG_DEPR	Placebo	114	2.62	3.37	0.12	3.45	<.001
	Olz	220	2.76	3.40	-0.60	3.33	(.474)
CG_MANIA	Placebo	114	4.33	0.79	-1.20	1.79	.001
	Olz	220	4.44	0.79	-3.48	1.25	(.399)
CG_OVER	Placebo	114	4.38	0.73	-0.89	1.11	.001
	Olz	220	4.30	0.74	-1.20	1.26	(.478)
MAN21TO	Placebo	114	13.94	7.83	-0.89	4.90	<.001
	Olz	220	14.52	8.46	-4.90	7.41	(.968)
PANNEG	Placebo	114	11.99	0.88	-0.44	4.39	.001
	Olz	220	12.43	1.11	-1.54	4.60	(.734)
PANPOS	Placebo	114	14.00	0.94	-1.13	4.04	.001
	Olz	220	15.45	4.85	-4.93	4.08	(.427)
PANSTOT	Placebo	114	41.75	15.51	-4.94	14.39	.001
	Olz	220	42.10	17.30	-12.90	19.72	(.334)
YMGSTOT	Placebo	114	22.47	8.15	-9.10	9.36	.001
	Olz	220	23.31	9.39	-11.13	8.93	(.443)

The following investigators were pooled: (011 020 034 036 041 043) and (095 000 020 023 024)

IMP.F1D.OCLIS(AS010000)

IMP.F1D.SANMAGD(S010000)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): P00C GLM model with treatment, and interaction.

Least-squares mean option in P00C GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

GLOSSARY

Legend of Variable Abbreviations:

Abbrev.	Description
CG_DEPR	CGI-20 Severity of Depression
CG_MANIA	CGI-20 Severity of Mania
CG_OVER	CGI-20 sev. of Overall Bipolar Illness
MAN21TO	MANO-21 Total Score
PANNEG	PANAS Negative Score
PANPOS	PANAS Positive Score
PANSTOT	PANAS Total Score
YMGSTOT	YMRS Total Score

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I believe that HGFU overall is a positive study. Study 1 although generally positive throughout just misses on the primary efficacy variable with a $p=.051$. Study 2 and the combined studies are positive.

Ohidul Siddiqui, statistical reviewer reached the following conclusions (please see statistical review).

“For the study#1, an additional analysis of the change from baseline to endpoint for the Y-MRS total score was performed after excluding enrolled patients from Investigator 021. This additional analysis was performed because Investigator 021 was discontinued due to noncompliance with good clinical practices. A total of 8 patients were enrolled at this site, with 6 patients randomized to receive Olz+MS treatment group, and 2 patients randomized to receive Pla+MS treatment group. After excluding the eight patients enrolled at this site from the final analysis, study#1 remained a positive study with respect to its primary efficacy result.”

“Based on the primary efficacy analyses (LOCF comparison of mean change from baseline to endpoint in Y-MRS total score) in each of the two studies, the superiority of Olz+MS over Pla+MS was indicated by a statistically significant difference between the treatment groups in the decrease in Y-MRS total score at endpoint. These results demonstrate the superiority of olanzapine added to lithium or valproate over placebo added to lithium or valproate in the acute treatment of acute mania.

In conclusion, olanzapine added to mood stabilizer therapy for the treatment of acute manic or mixed bipolar episodes, with or without psychotic features, was effective at a dose of 5, 10, 15 or 20 mg/day over the 6-week acute phase.”

D. Efficacy Conclusions

I believe that the two part study HGFU provides evidence to support this application for combination therapy adding olanzapine 5-20 mg/day to lithium or valproate for the treatment of acute mania.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

I believe that studies HGFU and HGGB along with the lack of any significant adverse findings in the literature search and post marketing review provide reasonable evidence of safety for olanzapine used in combination therapy with lithium or valproate for the treatment of acute

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mania. I would however point out in labeling that combination therapy exposes the patient to a higher rate of side effects, i.e. somnolence, peripheral edema and weight gain, than mood stabilizer used alone.

B. Description of Patient Exposure

The analyses of HGFU evaluated 344 randomized patients, with 229 patients (119 in Study 1 and 110 in Study 2) treated with olanzapine added to current mood stabilizer (Olz+MS) and 115 patients (56 in Study 1 and 59 in Study 2) treated with placebo added to current mood stabilizer (Pla+MS), following a 2:1 randomization allocation. At enrollment, 226 patients were being treated with valproate as a mood stabilizer and 117 were undergoing treatment with lithium; 1 patient was categorized as unspecified due to use of both mood stabilizers during the acute phase.

**Table HGFU.12.1. Patient Exposure to Olanzapine Therapy
Modal Daily Dose
F1D-MC-HGFU Studies 1 and 2 Combined**

Duration (Days)	Dose Range					Total	[N]	
	<5 mg	5 - <10 mg	10 - <15 mg	15 - <20 mg	>=20 mg			
<=7	2	1	14	2	0	19	(8.5%)	
7< - 14	2	1	2	0	0	5	(2.7%)	
14< - 21	0	1	0	3	2	6	(3.3%)	
21< - 28	0	1	0	2	0	3	(1.8%)	
28< - 35	0	2	2	3	0	7	(3.4%)	
35< - 42	0	23	20	11	11	65	(37.1%)	
>42	0	19	35	7	15	76	(32.8%)	
Total	9	58	105	18	28	218		
[N]	(2.2%)	(26.6%)	(48.2%)	(12.8%)	(12.8%)			
Total patient days of exposure:		7302						

Thirty-one of these patients completed the extension phase. The total exposure to olanzapine and to placebo was 15,677 patient days and 11,674 patient days, respectively.

C. Methods and Specific Findings of Safety Review

During both the acute and extension phases, safety evaluations for HGFU were based on records of vital signs, adverse events (unsolicited and solicited using the Association for Methodology and Documentation in Psychiatry [AMDP-5]), extrapyramidal symptoms, electrocardiograms, and laboratory tests. Measures for extrapyramidal symptoms included the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS).

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Acute Phase

During the acute phase, data from both studies were combined. The safety of olanzapine versus placebo added to mood stabilizer was evaluated in 344 randomized patients for 6 weeks of therapy (229 patients in the Olz+MS treatment arm, 115 patients in the Pla+MS treatment arm). Of these 344 patients, 242 patients completed the acute phase. The total exposure to olanzapine and to placebo was 7903 patient days and 4355 patient days, respectively.

Deaths

There was one patient, in Study 1, who died prior to receiving any study drug (34-0801).

Serious Adverse Events

Listings of patients who had serious adverse events which occurred during the study (including poststudy serious adverse events which occurred within 30 days of study discontinuation) from the acute period were reported to the sponsor as of the November 10, 1999 data cutoff date. Follow-up information received on Patients 12-0659 and 36-1659 was received after the November 10, 1999 cutoff date and is therefore not found in the Summary of Serious Adverse Events (Table HGFU.14.29).

Serious events are summarized in (Table HGFU.14.29). All the events were considered serious because they caused hospitalization or were considered life-threatening. Fifteen Olz+MS-treated patients experienced a total of 24 serious adverse events (17 different types of serious adverse events). Six Pla+MS-treated patients experienced a total of 7 serious adverse events (6 different types of serious adverse events). None of the rates of serious adverse events showed a statistically significant difference between the Olz+MS and Pla+MS treatment groups.

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**Table HGFU.14.29. Summary of Serious Adverse Events
F1D-MC-HGFU Studies 1 and 2 Combined**

SERIOUS ADVERSE EVENTS	Placebo			Ols			Fisher's Exact
	N	n	%	N	n	%	p-Value
DEPRESSION	115	2	1.7%	229	5	2.2%	1.00
AGITATION	115	1	0.9%	229	1	0.4%	1.00
EUPHORIA	115	1	0.9%	229	0	0.0%	.334
HALLUCINATIONS	115	1	0.9%	229	0	0.0%	.334
HOSTILITY	115	1	0.9%	229	1	0.4%	1.00
OVERDOSE	115	1	0.9%	229	2	0.9%	1.00
ANXIETY	115	0	0.0%	229	1	0.4%	1.00
CONFUSION	115	0	0.0%	229	1	0.4%	1.00
CONVULSION	115	0	0.0%	229	1	0.4%	1.00
DIABETES MELLITUS	115	0	0.0%	229	1	0.4%	1.00
EMOTIONAL LABILITY	115	0	0.0%	229	1	0.4%	1.00
GASTROINTESTINAL HEMORRHAGE	115	0	0.0%	229	1	0.4%	1.00
GRAND MAL CONVULSION	115	0	0.0%	229	1	0.4%	1.00
HICCUP	115	0	0.0%	229	1	0.4%	1.00
INSOMNIA	115	0	0.0%	229	1	0.4%	1.00

(CONTINUED)

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**Table HGFU.14.29. Summary of Serious Adverse Events
F1D-MC-HGFU Studies 1 and 2 Combined (concluded)**

SERIOUS ADVERSE EVENTS	Placebo			Ols			Fisher's Exact
	N	n	%	N	n	%	p-Value
MANIC REACTION	115	0	0.0%	229	3	1.3%	.554
MELENA	115	0	0.0%	229	1	0.4%	1.00
NERVOUSNESS	115	0	0.0%	229	1	0.4%	1.00
TREMOR	115	0	0.0%	229	1	0.4%	1.00

RMP.F1D5HGUFU.SASPGM(SAEQ01A)

RMS3040

ADVERSE EVENT DROP-OUTS

Twenty-five Ols+MS-treated patients discontinued because of an adverse event, and

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2 Pla+MS-treated patients discontinued because of an adverse event. Twice as many patients on placebo discontinued due to lack of efficacy. A tabulation of specific adverse events that led to discontinuation is found in Table HGFU.14.30.

**Table HGFU.10.12. Patient Disposition
F1D-MC-HGFU Studies 1 and 2 Combined**

Reason for Discontinuation	Placebo (N=115) n (%)	Ols (N=229) n (%)	Total (N=344) n (%)	p-Value*
Reporting Interval Complete	82 (71.3)	160 (69.9)	242 (70.3)	.804
Satisfactory Response	0	1 (0.4)	1 (0.3)	1.00
Adverse Event	2 (1.7)	25 (10.9)	27 (7.8)	.002
Lack of Efficacy	14 (12.2)	7 (3.1)	21 (6.1)	.002
Lost to Follow-up	3 (2.6)	5 (2.2)	8 (2.3)	1.00
Patient Decision	2 (1.7)	13 (5.7)	15 (4.4)	.159
Criteria not met / Compliance	5 (4.3)	12 (5.2)	17 (4.9)	.798
Sponsor Decision	1 (0.9)	1 (0.4)	2 (0.6)	1.00
Physician Decision	6 (5.2)	5 (2.2)	11 (3.2)	.191

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* Frequencies are analyzed using a Fisher's Exact test.
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Overall, statistically significantly more patients in the Olz+MS treatment group discontinued due to an adverse event (10.9%) than in patients in the Pla+MS treatment group (1.7%) (p=.002). Somnolence contributed most to this trend 6 OLA vs 0 PLA along with weight gain OLA 3 vs 0 PLA.

Table HGFU.14.31 is a listing of adverse events reported as reason for discontinuation.

**Table HGFU.14.30. Summary of Adverse Events Reported as Reason for Discontinuation
F1D-MC-HGFU Studies 1 and 2 Combined**

Event Classification	Placebo (N=115)		Olz (N=229)		p-Value*
	n	(%)	n	(%)	
PATIENTS DISCONTINUED	2	(1.7)	25	(10.9)	.002
AKATHISIA	0		1	(0.4)	1.00
AMBLYOPIA	0		1	(0.4)	1.00
CONVULSION	0		1	(0.4)	1.00
DEPRESSION	2	(1.7)	1	(0.4)	.260
DIABETES MELLITUS	0		1	(0.4)	1.00
EMOTIONAL LABILITY	0		1	(0.4)	1.00
GASTROINTESTINAL HEMORRHAGE	0		1	(0.4)	1.00
GRAND MAL CONVULSION	0		1	(0.4)	1.00
INCOORDINATION	0		1	(0.4)	1.00
INCREASED APPETITE	0		1	(0.4)	1.00
OVERDOSE	0		1	(0.4)	1.00
PERIPHERAL EDEMA	0		3	(1.3)	.554
RASH	0		1	(0.4)	1.00
SOMNOLENCE	0		6	(2.6)	.184
TWITCHING	0		1	(0.4)	1.00
WEIGHT GAIN	0		3	(1.3)	.554

TREATMENT-EMERGENT ADVERSE EVENTS

Twenty patients experienced nonserious potentially clinically significant adverse events. Treatment-emergent hyperglycemia was experienced in 2 patients in the Olz+MS treatment group (0.9%) compared to no patients in the Pla+MS treatment group. Treatment-emergent peripheral edema was experienced in 14 Olz+MS patients (6.1%) and in 4 Pla+MS patients (3.5%).

The most commonly reported treatment-emergent adverse events (10% incidence) in Olz+MS-treated patients were somnolence, dry mouth, weight gain, increased appetite, tremor, asthenia, depression, headache, dizziness, nervousness, diarrhea and thirst. In Pla+MS-treated patients, the most common events were somnolence, insomnia, headache, depression, diarrhea, nervousness, anxiety, asthenia, nausea, and tremor.

The treatment-emergent adverse events somnolence, dry mouth, weight gain, increased appetite, tremor, and speech disorder occurred statistically significantly more frequently in the Olz+MS treatment group than in the Pla+MS treatment group.

No clinically meaningful differences in electrocardiograms (ECGs), laboratory values,

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and vital signs were found between treatment groups. Weight gain was statistically significantly greater for the Olz+MS treatment group. There were no statistically significant mean changes from baseline to endpoint or from baseline to maximum score between treatment groups for Barnes Akathisia global score, Simpson-Angus total score, and Abnormal Involuntary Movement Scale (AIMS) total score.

In the bipolar mania combination placebo-controlled trials, the most commonly observed adverse events associated with the combination of olanzapine and lithium or valproate (incidence of $\geq 5\%$ and at least twice placebo) were: dry mouth (32% for olanzapine combination vs 9% for placebo), weight gain (26% vs 7%), increased appetite (24% vs 8%), dizziness (14% vs 7%), back pain (8% vs 4%), constipation (8% vs 4%), speech disorder (7% vs 1%), increased salivation (6% vs 2%), amnesia (5% vs 2%), and paresthesia (5% vs 2%).

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥ 5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

Table 2
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Combination Clinical Trials¹

Body System/Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine with lithium or valproate (N=229)	Placebo with lithium or valproate (N=115)
Body as a Whole		
Asthenia	18	13
Back pain	8	4
Accidental injury	4	2
Chest pain	3	2
Cardiovascular System		
Hypertension	2	1
Digestive System		
Dry mouth	32	9
Increased appetite	24	8
Thirst	10	6
Constipation	8	4
Increased salivation	6	2
Metabolic and Nutritional Disorders		
Weight gain	26	7
Peripheral edema	6	4
Edema	2	1
Nervous System		
Somnolence	52	27
Tremor	23	13

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Depression	18	17
Dizziness	14	7
Speech disorder	7	1
Amnesia	5	2
Paresthesia	5	2
Apathy	4	3
Confusion	4	1
Euphoria	3	2
Incoordination	2	0
Respiratory System		
Pharyngitis	4	1
Dyspnea	3	1
Skin and Appendages		
Sweating	3	1
Acne	2	0
Dry skin	2	0
Special Senses		
Amblyopia	9	5
Abnormal vision	2	0
Urogenital System		
Dysmenorrhea ²	2	0
Vaginitis ²	2	0

1 Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, abnormal dreams, abnormal ejaculation, agitation, akathisia, anorexia, anxiety, arthralgia, cough increased, diarrhea, dyspepsia, emotional lability, fever, flatulence, flu syndrome, headache, hostility, insomnia, libido decreased, libido increased, menstrual disorder², myalgia, nausea, nervousness, pain, paranoid reaction, personality disorder, rash, rhinitis, sleep disorder, thinking abnormal, vomiting.

2 Denominator used was for females only (olanzapine, N=128; placebo, N=51).

Extension Phase

Patients who completed the acute phase of the HGFU protocol and were considered responders were rerandomized to a double-blind therapy phase for an additional 18 months of therapy. The safety of these patients was evaluated in 136 randomized patients (72 patients in the Olz+MS treatment arm, 64 patients in the Pla+MS treatment arm). Thirty-one of these patients completed the extension phase. The total exposure to olanzapine and to placebo in the extension phase was 15,677 patient days and 11,674 patient days, respectively.

The safety of olanzapine versus placebo added to mood stabilizer therapy for the extension phase was evaluated in 99 patients who had been randomized to olanzapine in the acute phase. Following a 1:1 rerandomization allocation in the extension phase, 51 patients were treated with Olz+MS, and 48 patients were treated with Pla+MS. Of

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these 99 patients, 21 patients completed the extension phase of the study. The total exposure to olanzapine and to placebo in the extension phase was 11,329 patient-days and 8222 patient-days, respectively. The median and mean modal daily doses of olanzapine were 10.0 mg/day and 8.6 mg/day, respectively.

There were no patient deaths during the extension phase of the study.

A listing of patients who had serious adverse events during the extension phase of the study and reported to the sponsor (including poststudy serious adverse events which occurred within 30 days of study discontinuation from the extension period and were reported to the sponsor as of the November 30, 2000 data cutoff date) is found below.

Table HGFU.14.23. Summary of Serious Adverse Events Patients for Patients Randomized to Olanzapine in the Acute Phase and Rerandomized After Acute Therapy F1D-MC-HGFU, Study Period III

SERIOUS ADVERSE EVENTS	Placebo			Ols			Fisher's Exact
	N	n	%	N	n	%	p-Value
THINKING ABNORMAL	48	1	2.1%	51	1	2.0%	1.00
DRUG DEPENDENCE	48	0	0.0%	51	1	2.0%	1.00
HOSTILITY	48	0	0.0%	51	1	2.0%	1.00
PARANOID REACTION	48	0	0.0%	51	1	2.0%	1.00
SOMNOLENCE	48	0	0.0%	51	1	2.0%	1.00
ABDOMINAL PAIN	48	1	2.1%	51	0	0.0%	.485
ANESTHESIA	48	1	2.1%	51	0	0.0%	.485
ANEMIA	48	1	2.1%	51	0	0.0%	.485
CHOLELITHIASIS	48	1	2.1%	51	0	0.0%	.485
DEPRESSION	48	1	2.1%	51	0	0.0%	.485
DIARRHEA	48	1	2.1%	51	0	0.0%	.485
GASTROINTESTINAL HEMORRHAGE	48	1	2.1%	51	0	0.0%	.485
MANIC REACTION	48	1	2.1%	51	0	0.0%	.485
MARROW DEPRESSION	48	1	2.1%	51	0	0.0%	.485
NERVOUSNESS	48	1	2.1%	51	0	0.0%	.485
PSYCHOSIS	48	1	2.1%	51	0	0.0%	.485
SUICIDE ATTEMPT	48	1	2.1%	51	0	0.0%	.485

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Table HGFU.14.24. Summary of Serious Adverse Events Reported as Reason for Discontinuation Patients for Patients Randomized to Olanzapine in the Acute Phase and Rerandomized After Acute Therapy F1D-MC-HGFU, Study Period III

Event Classification	Placebo (N=48)		Olx (N=51)		p-Value*
	n	(%)	n	(%)	
PATIENTS DISCONTINUED	8	(16.7)	5	(9.8)	.380
AKATHISIA	1	(2.1)	1	(2.0)	1.00
ALOPECIA	1	(2.1)	0		.485
ASTHENIA	0		1	(2.0)	1.00
CREATINE PHOSPHOKINASE INCREASED	0		1	(2.0)	1.00
DEPRESSION	2	(6.3)	0		.110
MANIC REACTION	1	(2.1)	0		.485
NARROW DEPRESSION	1	(2.1)	0		.485
SOMNOLENCE	1	(2.1)	0		.485
WEIGHT GAIN	0		2	(3.9)	.495

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Of the patients rerandomized after receiving olanzapine in the acute phase, 3 Olz+MS-treated patients experienced a total of five serious adverse events (five different types of serious adverse events) and 6 Pla+MS-treated patients experienced 13 serious adverse events (13 different types of serious adverse events). However, there were no statistically significant differences between treatment groups in the rates of any serious adverse event.

Of the patients rerandomized after receiving olanzapine therapy in the acute phase, 5 Olz+MS-treated patients, and 8 Pla+MS-treated patients discontinued because of an adverse event. There were no statistically significant differences between treatment groups in the frequency of discontinuations due to adverse events either overall or for any specific adverse event.

The treatment-emergent adverse event insomnia occurred statistically significantly more frequently in the Pla+MS treatment group than in the Olz+MS treatment group. The treatment-emergent adverse events somnolence, weight gain, and decreased libido occurred statistically significantly more frequently in the Olz+MS treatment group than in the Pla+MS treatment group.

The most commonly reported treatment-emergent adverse events (10% incidence) in Olz+MS-treated patients were depression, somnolence, weight gain, anxiety, and tremor. In Pla+MS-treated patients, the most common events were depression, anxiety, apathy, asthenia, diarrhea, insomnia, and thinking abnormal.

No clinically meaningful changes in ECGs, laboratory values, and vital signs were found

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between treatment groups. Weight gain was significantly greater for the Olz+MS treatment group.

Analysis of laboratory assessments showed statistically significant differences between treatment groups in change from baseline to endpoint for MCH and platelet count. These changes were not considered to be clinically significant. There were no statistically significant differences between treatment groups in the incidence rates of treatment-emergent abnormal, high, or low laboratory values at any time during the extension phase.

In the analysis of mean change from baseline to endpoint in vital signs and weight, and in the analysis of potentially clinically significant changes in vital signs and weight, a statistically significant difference between treatment groups was observed for weight gain. Patients in the Olz+MS treatment group had a mean weight gain from baseline to endpoint of 2.00 kg compared to a mean weight decrease of 1.82 kg in the Pla+MS treatment group ($p < .001$). Potentially clinically significant weight gain (10% or more of baseline weight) was observed in 19.6% and 2.1% of patients in the Olz+MS group and Pla+MS group, respectively ($p = .008$).

In the analysis of mean change from baseline to endpoint for ECG heart rate and interval times (PR, QRS, QT, and Bazett-corrected and Fridericia-corrected QT), there were no statistically significant differences between the Olz+MS and Pla+MS treatment groups. In the analysis of potentially clinically significant changes in ECG interval times and heart rate, including six additional criteria specific to potentially prolonged ECG QTc intervals based on both Bazett's and Fridericia's corrections, there were no statistically significantly different incidence rates between the Olz+MS treatment group and the Pla+MS treatment group.

There was a statistically significant difference between treatment groups in the mean change from baseline to endpoint in AIMS total score, with a mean decrease of 0.02 in Olz+MS-treated patients and a mean increase of 0.13 in Pla+MS-treated patients ($p = .027$). There was a statistically significant difference between treatment groups in the mean change from baseline to endpoint in Simpson-Angus total score, with a mean increase of 0.22 in Olz+MS-treated patients and a mean decrease of 0.13 in Pla+MS-treated patients ($p = .015$). In contrast, in the analysis of treatment-emergent abnormalities based on the Simpson-Angus total scores, there were no statistically significant treatment differences. Furthermore, no statistically significant differences were found for treatment-emergent adverse events based on the Barnes Akathisia global scores and AIMS total scores.

In summary, there were no clinically significant changes in vital signs, laboratory analytes, ECGs and heart rate, or extrapyramidal symptoms, with the exception of potentially clinically significant weight gain (10% or more of baseline weight) in 19.6% of patients in the Olz+MS group.

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See table HGFU.12.1 for patient exposure below.

Table HGFU.12.1. Patient Exposure to Olanzapine Therapy
Modal Daily Dose
Patients Randomized to Olanzapine in the Acute Phase and Rerandomized After Acute Therapy
F1D-MC-HGFU, Study Period III

Duration (Days)	Dosage Range					Total	(%)
	<5 mg	5 - <10 mg	10 - <15 mg	15 - <20 mg	>=20 mg		
<=7	0	1	0	0	0	1	(2.0%)
7< - 14	0	0	3	0	0	3	(5.9%)
14< - 28	0	2	2	0	0	4	(7.8%)
28< - 56	1	2	3	0	1	7	(13.7%)
56< - 112	0	5	2	4	0	11	(21.6%)
112< - 168	0	3	0	0	0	3	(5.9%)
168< - 224	0	2	1	0	1	4	(7.8%)
224< - 280	0	0	0	0	1	1	(2.0%)
280< - 336	0	0	0	0	0	0	
336< - 392	0	0	1	0	0	1	(2.0%)
392< - 448	0	0	0	0	0	0	
>=448	0	7	9	0	0	16	(31.4%)
Total	1	22	21	4	3	51	
(%)	(2.0%)	(43.1%)	(41.2%)	(7.8%)	(5.9%)		

Total patient days of exposure: 11329

Pharmacokinetic Study

HGGB (see biopharm review for additional details of review)

Study HGGB evaluated the potential for pharmacokinetic and pharmacodynamic drug interactions between olanzapine and valproate in patients with bipolar or schizoaffective disorder after having been stabilized on valproate for 2 months. Olanzapine co-administered with valproate for 2 weeks was compared with placebo co-administered with valproate. HGGB was designed as a 2-part multisite study. Part A, which involved patients with bipolar or schizoaffective disorder stabilized on divalproex for 2 months, was designed as a parallel comparison of olanzapine versus placebo co-administered with divalproex. Part B, which involved patients with bipolar disorder meeting the inclusion criteria/exclusion criteria of HGFU, was designed for competitive enrollment with Part A. Patients enrolled in Part B had completed HGFU.

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Interim Clinical Study Synopsis: Study F1D-LC-HGGB

Title: Olanzapine - Divalproex Sodium/Valproic Acid Interaction Trial

Investigators: John T. Callaghan, MD, pH, Lilly Laboratory for Clinical Research, Indianapolis, IN 46202

Study Centers: There were 5 study centers.

Dates of Study: June 1997 through January 2000

Clinical Phase: Phase I

Objectives: Part A: To determine any pharmacokinetic or pharmacodynamic drug interaction, safety, physiologic disposition; to assess effects of single and multiple doses of olanzapine on steady-state valproic acid concentrations; and to evaluate neuroendocrine effects during coadministration of divalproex sodium (hereafter designated as divalproex) and olanzapine.
Part B: To determine any pharmacokinetic drug interaction during coadministration of divalproex/valproic acid (hereafter, designated as divalproex) and olanzapine, to determine physiologic disposition of multiple-dose divalproex on olanzapine concentration profiles, and to assess the effects of multiple doses of olanzapine on steady-state valproic acid concentrations.

Methodology: Two-part multisite study. Part A was designed as a parallel comparison of olanzapine versus placebo coadministered with divalproex. Part B was designed for competitive enrollment with Part A and was a parallel comparison of olanzapine versus placebo coadministered with divalproex from patients with bipolar illness obtained from Study F1D-MC-HGFU.

Number of Patients: (Part A) Male 20, Female 22, Total 42 (Only one patient from the HGFU trial enrolled in HGGB. Part B was stopped when all the necessary patients were enrolled in Part A.)

Diagnosis and Inclusion Criteria: Patients with bipolar or schizoaffective disorder stabilized on divalproex for 2 months. Males or females between the ages of 18 and 65 years, inclusive; on a stable dose of divalproex sodium

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(50-125 µg/mL) and possibly on a stable dose of lithium (0.6 mEq/L). Have given written informed consent.

Dosage and Administration: Divalproex— An individualized dosage (500 to 2250 mg per day) which maintained valproic acid plasma concentrations within the therapeutic range (50-125 µg/mL).
Olanzapine— 10 mg as a single dose and then as a multiple dose regimen of 10 mg once daily for approximately 2 weeks
Olanzapine 10-mg tablets (CT04017, CT10117, CT11817),
Olanzapine placebo (CT08802, CT08960, CT10215)
Treatment Group— Divalproex stable dosage regimen to which olanzapine (Group 1) or placebo (Group 2) was added

Duration of Treatment: Divalproex— Daily regimen maintained throughout the study
Olanzapine— Single dose; multiple dose approximately 2 weeks

Criteria for Evaluation: Safety— Comparisons between treatment groups for the QTc and prolactin values were performed during the olanzapine-divalproex treatment group versus the placebo-divalproex group. Liver tests were evaluated for evidence of clinically significant liver injury.
Pharmacokinetic— Plasma concentrations of valproic acid and olanzapine were used to assess the potential effects of each drug upon the other. Excretion of valproic acid in urine was assessed.
Pharmacodynamic— CGI-BP and alertness assessments were evaluated during olanzapine-divalproex coadministration and compared with assessments during placebo-divalproex.

Methods: Bioanalytical— [] human plasma samples were analyzed for olanzapine before and after [] using a validated HPLC method. Local laboratories were used to provide valproic acid plasma concentrations for therapeutic monitoring (standard CLIA methodologies). Additional plasma and urine samples were analyzed for valproic acid concentration using a centralized laboratory.
Pharmacokinetic— Noncompartmental methods were applied to olanzapine plasma concentration data. Valproic acid plasma data were assessed graphically and by statistical analysis.
Statistical— For pharmacodynamic and ECG measures, an omnibus analysis was conducted based on a statistical model that accounted for treatment group, measurement session, and the interaction of group-by-session as sources of variability. Significant findings elicited in the omnibus analysis were further examined by comparing the treatment groups at each measurement session separately. Since the CGI scores are multinomial, contingency table analyses were conducted by measurement session to compare treatments. Comparisons between treatments for local and central laboratory valproic acid

Sponsor's Summary and Conclusions:

- *The combination of olanzapine and valproic acid under the conditions of this study appeared safe.*
- *Comparisons between treatment groups for the QTc showed no statistically significant differences.*
- *Prolactin values were increased during the olanzapine-divalproex treatments in comparison to the placebo-divalproex treatments.*

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- The combination of valproic acid and olanzapine did not produce evidence of clinically significant liver or hematologic injury.*
- Clinical deterioration in the psychiatric state of these patients was not observed for either the olanzapine or placebo group during the course of the study.*
- Valproic acid concentrations were not significantly different between the treatment groups and fell within the targeted therapeutic range. The dosage of divalproex was changed in only one patient.*
- Olanzapine pharmacokinetics were similar to characteristic values for the drug given alone.*
- The data from this study show that there is neither a pharmacokinetic nor a pharmacodynamic interaction between divalproex sodium and olanzapine.*
- Although good medical practice typically includes VPA drug concentration monitoring for patients being treated with divalproex, results of this study suggest that additional or extraordinary VPA drug concentration monitoring is not warranted if olanzapine is simply added to the therapeutic agents being used in patients with previously stable valproic acid concentrations.*

Safety Review

Study HGGB evaluated the potential for pharmacokinetic and pharmacodynamic drug interactions between olanzapine and valproate in patients with bipolar or schizoaffective disorder after having been stabilized on valproate for 2 months. Olanzapine co-administered with valproate for 2 weeks was compared with placebo co-administered with valproate. Clinical deterioration in the psychiatric state of these patients (as measured by the CGI mania, depression, and bipolar scores) was not observed for either treatment. Plasma concentrations of valproic acid were not affected by co-administration of olanzapine. The overall pharmacokinetic interaction between olanzapine and valproate characteristics did not suggest a need to alter the typical dosages prescribed for either agent.

There were no deaths, serious or nonserious clinically significant adverse events. Two patients (2001 and 6001) were discontinued due to adverse events. No clinically meaningful changes in ECGs, laboratory values, and vital signs were found in either treatment group. Please see biopharm review.

Comparisons between treatment groups for the QTc (Bazett correction) showed no statistically significant differences. However, 1 female patient (5008) given olanzapine had a posttreatment QTc interval >450 msec (actual value = 452.8 msec); the QTc was prolonged >30 msec (actual value = 44.2) more than her averaged control value. The patient was also treated with Zoloft daily. This observation was noted only after single-dose olanzapine and not after multiple-dose.

Prolactin values were increased during the olanzapine- divalproex treatment group in comparison to the placebo-divalproex group. The increase was not associated with

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clinical findings.

Minor transient elevations (generally <2X ULN) in liver enzymes occurred in 4 patients treated with olanzapine/valproic acid and in 2 patients treated with placebo/valproic acid. In 5 other patients (3 on olanzapine and 2 on placebo) the abnormalities were attributed to pre-existing and ongoing hepatic injury. Nonreversible injury patterns occurred in 1 untreated patient and 3 patients with pre-existing liver injury patterns and were not attributed to the study drugs. These observations were not associated with elevations in alkaline phosphatase or bilirubin. The combination of valproic acid and olanzapine did not produce evidence of clinically significant liver injury.

FOREIGN SAFETY LABELING CHANGES

The sponsor has provided a summary of foreign safety labeling changes which I include below.

All safety labeling changes for Australia, Canada, Europe, Japan, and New Zealand are listed below. These changes occurred after the last submission to the NDA (20-592) in December of 1999.

Table 3.4. Changes in the European Summary of Product Characteristics

Type of Change	Submission Date	CPMP Opinion	Commission Decision	Description of Change
Safety variation to SPC arising from assessment of PSUR 3 (PSUR 3: 25 May 1998)	23 Dec 98	21 Apr 99	19 Jul 99	Sections 4.4 and 4.8: Add hyperglycaemia/exacerbation of preexisting diabetes Section 4.5: Add fluoxetine interaction statement Section 4.8: Priapism
Safety variation to SPC arising from assessment of PSUR5 (PSUR5: 17 Jan 2000)	23 Dec 99	24 May 00	25 Sep 00	Section 4.5: Add fluvoxamine interaction Section 4.8: Abnormal gait in patients with Alzheimer's disease Section 4.8: Bradycardia
Safety variation to SPC at request of CPMP	19 Jun 00	21 Sep 00	28 Dec 00	Section 4.4: Paragraph on hyperglycaemia moved to top of Section 4.4; added terms acidosis and coma Section 4.4: Reference made to cases of hepatitis with advice for discontinuation Section 4.8: Term "peripheral" is deleted before "oedema" Section 4.8: Hyperglycaemia information moved from under "Rare<1%" to "Occasional 1-10%" Section 4.9: Overdose information rewritten in line with clinical experience.
Safety variation to SPC	5 Dec 00	28 Feb 01	14 Jun 01	Section 4.8: Clarification of clinical trial information on hyperglycaemia; introduced CIOMS category (<0.01% very rare) for spontaneous reports of hyperglycaemia (with/without ketoacidosis or coma), hepatitis, and priapism.

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Table 3.5 Changes to the Japanese Package Insert

Section of Label	Change to Physician Insert
Warnings	Accompanying marked increase in blood glucose, serious adverse reactions such as diabetic ketoacidosis, diabetic coma, etc., may appear leading potentially to death. Observe sufficiently such as measurement of blood glucose during the olanzapine administration.
	Upon administration, explain sufficiently in advance to patients and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately if such symptoms appear. (See the section on "Important Precautions" in Attachment 4)
Contraindication	Patients with diabetes mellitus and those who have a history of diabetes mellitus.
Careful Administration	Patients with risk factors for diabetes mellitus such as family history of diabetes mellitus, hyperglycemia, obesity, etc. (See the section on "Important Precautions" in Attachment 4).
Important Precaution	By administration of this drug, marked increase in blood glucose may appear leading to fatal clinical course such as diabetic ketoacidosis, diabetic coma, etc. Observe sufficiently such as measurement of blood glucose during the olanzapine administration. In particular, patients with risk factors for diabetes mellitus such as hyperglycemia, obesity, etc., blood glucose may increase leading to acute worsening of metabolic state.
	Upon administration, explain sufficiently in advance to patients and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately if such symptoms appear.
Clinically Significant Adverse Reactions	Hyperglycemia, diabetic ketoacidosis, diabetic coma: Hyperglycemia may develop leading to fatal clinical course, such as diabetic ketoacidosis and diabetic coma leading to death. Thus, make a close observation, such as blood glucose measurement, (appearance of) thirst, polydipsia, polyurea, frequent urination. If any abnormalities are noted, discontinue administration and take an appropriate measure(s), including administration of insulin.

Drug Abuse Potential and Overdose

Drug Abuse Potential

The sponsor reports they are unaware of any new substantive data from the studies in this submission that would alter the drug abuse potential for the oral olanzapine formulations (NDA 20-592 olanzapine tablets, NDA 21-086 olanzapine orally disintegrating tablets).

Overdose

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No instances of overdose (intended or accidental) with olanzapine occurred during any of the oral olanzapine studies in this submission and the sponsor reports they are unaware of any new substantive data that would alter the available overdose information for oral olanzapine.

D. Adequacy of Safety Testing

The Division agreed that achieving positive results in a single study evaluating the efficacy of olanzapine compared with placebo when each is added to lithium or valproate would be adequate for an adjunctive therapy acute mania claim.

I feel the safety evaluation for olanzapine used in combination with valproate or lithium is adequately presented.

E. Summary of Critical Safety Findings and Limitations of Data

The data appear to be adequate to support this submission. Please see recommendations for labeling suggestions.

VIII. Dosing, Regimen, and Administration Issues

During HGFU Study Period II, patients received either olanzapine 5, 10, 15, or 20 mg/day or placebo. This dose range was chosen to determine the most efficacious dose in the treatment of mania associated with bipolar I disorder, and was consistent with approved dosages in the treatment of schizophrenia and related psychotic disorders. Dose-response was not evaluated within this range.

Modal dosing for study HGFU is presented below.

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**Table HGFU.11.150. Modal Drug Dosage
F1D-MC-HGFU Studies 1 and 2 Combined**

	Placebo	Clanzapina
Number of Patients (%)		
0.0 mg	115 (100.0%)	5 (2.2%)
5.0 mg	0	58 (25.9%)
10.0 mg	0	105 (46.9%)
15.0 mg	0	28 (12.5%)
20.0 mg	0	28 (12.5%)
Total	115	224
Dosage (mg)		
Mean	0.0	10.4
Modal	0.0	10.0
Median	0.0	10.0
Std. Dev.	0.0	4.9

No drug concentration information was collected.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Subgroup analyses were performed to examine the consistency of treatment effects over the strata of various demographic populations. The stratifying characteristics included in these analyses were age (<40 years, ≥40 years), gender, ethnic origin (Caucasian, other), mood stabilizer therapy (lithium or valproate), psychotic vs nonpsychotic features, bipolar mixed vs bipolar manic, presence or absence of a rapid cycling course, previous lithium exposure, previous valproate exposure, previous exposure to antipsychotic medications, and concomitant benzodiazepine use. A subgroup was analyzed only if the number of patients in each strata was 10 or more.

For the Y-MRS total score, there were no statistically significant treatment-by-subgroup interactions. Please see individual subgroups in table to follow.

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**Table HGFU.11.149. Summary of Specific Subgroup Analyses
F1D-MC-HGFU Studies 1 and 2 Combined**

Subgroup	N (Olanzapine:Placcho)	Treatment Comparisons
Age <40	105:63	Y-MRS total (p=.001) HAMD-21 total (p<.001) PANSS total (p=.001)
Age ≥40	115:51	HAMD-21 total (p=.003)
Female	123:51	Y-MRS total (p=.033) HAMD-21 total (p=.002)
Male	97:63	Y-MRS total (p=.001) HAMD-21 total (p<.001) PANSS total (p<.001)
Caucasian	188:96	Y-MRS total (p<.001) HAMD-21 total (p<.001) PANSS total (p=.002)
Lithium as mood stabilizer	74:41	HAMD-21 total (p=.005) PANSS total (p=.017)
Valproate as mood stabilizer	146:72	Y-MRS total (p<.001) HAMD-21 total (p<.001) PANSS total (p=.002)
With current psychotic features	70:38	HAMD-21 total (p<.001)
Without current psychotic features	150:76	Y-MRS total (p<.001) HAMD-21 total (p<.001) PANSS total (p=.005)
Manic episode	99:60	HAMD-21 total (p=.006)
Mixed episode	121:54	Y-MRS total (p<.001) HAMD-21 total (p<.001) PANSS total (p=.001)
Not in a rapid cycling course	122:61	Y-MRS total (p=.003) HAMD-21 total (p=.014) PANSS total (p=.011)

continued

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Table 11.149. (concluded) Summary of Specific Subgroup Analyses F1D-MC-HGFU Studies 1 and 2 Combined

Subgroup	N (Olanzapine:Placebo)	Treatment Comparisons
Rapid cycling course	98:53	Y-MRS total (p=.001) HAMD-21 total (p<.001) PANSS total (p=.009)
No previous exposure to lithium	66:28	Y-MRS total (p=.002)
Nonresponder to previous lithium exposure	76:41	Y-MRS total (p=.013) HAMD-21 total (p<.001) PANSS total (p=.002)
Responder to previous lithium exposure	78:45	Y-MRS total (p=.009) HAMD-21 total (p<.001) PANSS total (p=.001)
No previous exposure to valproate	54:27	Y-MRS total (p=.004) PANSS total (p=.003)
Nonresponder to previous valproate exposure	60:41	HAMD-21 total (p=.003)
Responder to previous valproate exposure	106:46	Y-MRS total (p=.008) HAMD-21 total (p<.001) PANSS total (p=.029)
No previous exposure to an antipsychotic	121:61	Y-MRS total (p=.001) HAMD-21 total (p<.001) PANSS total (p=.002)
Nonresponder to previous antipsychotic exposure	37:23	HAMD-21 total (p=.012)
Responder to previous antipsychotic exposure	62:30	Y-MRS total (p=.014) HAMD-21 total (p=.008) PANSS total (p=.002)
No concomitant use of benzodiazepines	158:75	Y-MRS total (p=.019) HAMD-21 total (p=.018)
Concomitant use of benzodiazepines	62:39	Y-MRS total (p=.003) HAMD-21 total (p<.001) PANSS total (p=.004)

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B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There are no significant subgroup variations to report. See section above for efficacy sub group evaluations.

C. Evaluation of Pediatric Program

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

As a Phase 4 commitment for the bipolar mania monotherapy indication, Lilly is conducting a 3-week placebo-controlled study of olanzapine monotherapy in adolescent patients (ages 13 to 17 years) diagnosed with manic or mixed episode associated with bipolar I disorder (with or without psychotic features). However, Lilly does not intend to conduct studies in the pediatric population (ages birth to 17 years) to evaluate olanzapine in combination with lithium or valproate for the treatment of manic or mixed episodes associated with bipolar I disorder since a pediatric waiver was granted during the May 30, 2002 pre-NDA meeting (see FDA meeting minutes issued July 2, 2002).

The Division agreed that a study in pediatric patients evaluating olanzapine in combination with mood stabilizers in the treatment of bipolar mania would not be required and thus a pediatric waiver could be obtained.

D. Comments on Data Available or Needed in Other Populations

The Division indicated that achieving positive results in a single study evaluating the efficacy of olanzapine compared with placebo when each is added to lithium or valproate would be adequate for an adjunctive therapy acute mania claim. There is no requirement for testing in other populations.

X. Conclusions and Recommendations

A. Conclusions

I believe that the two part study HGFU provides evidence to support this application for combination therapy adding olanzapine to lithium or valproate for the treatment of acute mania. I feel the safety for olanzapine used in combination with valproate or lithium is adequately established. The combination does however expose the patient to a higher risk of treatment

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emergent adverse events in general and in particular to discontinuation due to either somnolence, peripheral edema or weight gain in the acute phase.

B. Recommendations

I recommend this supplement be approved for olanzapine combination therapy when added to lithium or valproate for the treatment of acute mania. []

In the current approved Zyprexa labeling, revised labeling text is proposed in the following sections: CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION. The majority of these changes are the customary language related to the new indication.

The rationales for additional sponsor revised labeling text are as follows:

“Under the *Clinical Efficacy Data* subsection of CLINICAL PHARMACOLOGY, the revised labeling proposes parenthetical inclusion of the symptoms corresponding to the 11 items from the Young Mania Rating Scale (Y-MRS), the primary efficacy scale in Protocol HGFU. Since launch of the bipolar mania monotherapy indication in April 2000, we have come to learn that prescribing clinicians are not as familiar with the Y-MRS as previously thought and thus we believe that inclusion of these symptoms would serve to further educate the prescribers.

Under the *Drug Interactions* subsection of PRECAUTIONS, the revised labeling proposes moving the currently approved reference of the results from the lithium clinical pharmacology study (E001; submitted September 21, 1995 with NDA 20-592) to its own sub-heading under this section. With the proposed registration of the use of olanzapine in combination with lithium or valproate, the new subheading would allow the reader to more easily find the pertinent interaction information.

Under the Incidence of Adverse Events in Short-Term, Placebo-Controlled Trials subsection of ADVERSE REACTIONS, the revised labeling proposes re-formatting the currently approved Commonly Observed Adverse Event tables for schizophrenia and bipolar mania into text. This formatting would be consistent with all other currently approved atypical antipsychotic labeling and would continue to convey pertinent safety information in labeling.”

Veneeta Tandon, Ph.D. in the biopharm review makes the following labeling comments.

“The following Labeling changes made by the sponsor in the Drug interaction Section under PRECAUTIONS are acceptable and should apply to both supplements 018 as well as 019. The original valproate section has been deleted and a new section has been added. Lithium has been

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given its own sub heading and has been removed from a list of general drugs that did not show interaction.

Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.

Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. In vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, [] ethanol, or biperiden. However, the co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.”

I have no objections to these proposed labeling changes. I would however point out in labeling that combination therapy exposes the patient to a higher rate of adverse effects in general and in particular to discontinuation from peripheral edema, somnolence and weight gain, than mood stabilizer used alone.

Table 2 in labeling demonstrates the increased adverse events observed in the combination. The sponsor gives the following information about discontinuation in the combination trials.

“Bipolar Mania Combination Therapy — []

I would change this to :

Bipolar Mania Combination Therapy — []

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Earl D. Hearst, M.D.
Medical Reviewer
HFD-120

CC:taughren,eharst,dbates,pandreason

XI. Appendix

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Table 2. MedDRA Preferred Terms Reported at a Rate Within Patients Treated Concomitantly with Mood Stabilizers of \geq Twice that Reported in Patients Not Treated Concomitantly with Mood Stabilizers with an Absolute Number of Cases with Mood Stabilizer Therapy of ≥ 6

MedDRA Preferred Term (MedDRA 4.0 Version)	Reporting Ratio (%) Within Patients Receiving Concomitant Mood Stabilizers	Reporting Ratio (%) Within Patients Not Receiving Concomitant Mood Stabilizers	Proportional Reporting Ratio (PRR)
Mania	1.49%	0.72%	2.07
Hostility	0.63%	0.25%	2.52
Short Term Memory Loss	0.25%	0.10%	2.5
Depression Suicidal	0.25%	0.06%	4.17
Mood Swings	0.22%	0.10%	2.2
Sleep Walking	0.25%	0.09%	2.78
Above 6 terms grouped together	3.09%	1.32%	2.34
Prescribed Overdose	2.40%	1.11%	2.16
Drug Interaction NOS	1.96%	0.75%	2.61
Drug Level NOS Increased	0.55%	0.25%	2.2
Anticonvulsant Drug Level NOS Below Therapeutic	0.39%	0.02%	19.5
Drug Toxicity NOS	0.36%	0.11%	3.27
Laboratory Test Abnormal NOS	0.33%	0.05%	6.6
Drug Level NOS Decreased	0.28%	0.01%	28
Antidepressant Drug Level NOS Above Therapeutic	0.22%	0.01%	22
Above 7 terms grouped together	4.09%	1.2%	3.41

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Table 2. MedDRA Preferred Terms Reported at a Rate Within Patients Treated Concomitantly with Mood Stabilizers of \geq Twice that Reported in Patients Not Treated Concomitantly with Mood Stabilizers with an Absolute Number of Cases with Mood Stabilizer Therapy of ≥ 6 (continued)

MedDRA Preferred Terms (MedDRA 4.0 Version)	Reporting Ratio (%) Within Patients Receiving Concomitant Mood Stabilizers	Reporting Ratio (%) Within Patients Not Receiving Concomitant Mood Stabilizers	Proportional Reporting Ratio (PRR)
Blood Creatinine Increased	0.44%	0.12%	3.67
Renal Failure Acute	0.33%	0.11%	3.0
Blood Urea Increased	0.25%	0.09%	2.78
Renal Impairment NOS	0.19%	0.06%	3.17
Above 4 terms grouped together	1.21%	0.38%	3.18
Diabetic Ketoacidosis	0.83%	0.38%	2.18
Hypoglycaemia NOS	0.44%	0.18%	2.44
Ketoacidosis	0.30%	0.14%	2.14
Diabetic Coma NOS	0.28%	0.07%	4.0
Polyuria	0.69%	0.20%	3.45
Above 5 terms grouped together	2.54%	0.97%	2.62
Eosinophilia	0.44%	0.20%	2.2
Neutrophil Count Decreased	0.22%	0.10%	2.2
Body Temperature Increased	0.72%	0.28%	2.57
Hyperpyrexia	0.28%	0.11%	2.55
Above 4 terms grouped together	1.66%	0.69%	2.41
Peripheral Swelling	1.68%	0.78%	2.15
Pitting Edema	0.74%	0.23%	3.22
Above 2 terms grouped together	2.42%	1.01%	2.40

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Table 2. MedDRA Preferred Terms Reported at a Rate Within Patients Treated Concomitantly with Mood Stabilizers of \geq Twice that Reported in Patients Not Treated Concomitantly with Mood Stabilizers with an Absolute Number of Cases with Mood Stabilizer Therapy of ≥ 6 (continued)

MedDRA Preferred Term (MedDRA 4.0 Version)	Reporting Ratio (%) Within Patients Receiving Concomitant Mood Stabilizers	Reporting Ratio (%) Within Patients Not Receiving Concomitant Mood Stabilizers	Proportional Reporting Ratio (PRR)
Ataxia	0.52%	0.14%	3.71
Coordination Abnormal NOS	0.28%	0.09%	3.11
Neck Stiffness	0.39%	0.15%	2.6
Neck Pain	0.17%	0.07%	2.43
Cogwheel Rigidity	0.39%	0.16%	2.44
Gait Festinating	0.19%	0.09%	2.11
Above 6 terms grouped together	1.94%	0.70%	2.77
Pancreatitis Acute	0.17%	0.06%	2.83
Cholelithiasis	0.17%	0.04%	4.25
Encephalopathy NOS	0.17%	0.05%	3.4
Blood Amylase Increased	0.22%	0.08%	2.75
Above 4 terms grouped together	0.73%	0.23%	3.17
Blood Cholesterol Increased	0.72%	0.36%	2.0
Blood Pressure Increased	0.55%	0.25%	2.2
Incontinence NOS	0.36%	0.18%	2.0
Tinnitus	0.33%	0.14%	2.36
Respiratory Distress	0.30%	0.10%	3.0
Blood Thyroid Stimulating Hormone Increased	0.28%	0.05%	5.6
Facial Palsy	0.25%	0.10%	2.5
Hypothyroidism	0.22%	0.09%	2.44
Stupor	0.19%	0.08%	2.38

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Table 2. MedDRA Preferred Terms Reported at a Rate Within Patients Treated Concomitantly with Mood Stabilizers of \geq Twice that Reported in Patients Not Treated Concomitantly with Mood Stabilizers with an Absolute Number of Cases with Mood Stabilizer Therapy of ≥ 6 Cases (concluded)

MedDRA Preferred Term (MedDRA 4.0 Version)	Reporting Ratio (%) Within Patients Receiving Concomitant Mood Stabilizers	Reporting Ratio (%) Within Patients Not Receiving Concomitant Mood Stabilizers	Proportional Reporting Ratio (PRR)
Heart Rate Decreased	0.19%	0.06%	3.17
Heus Paralytic	0.19%	0.05%	3.8
Electrocardiogram T Wave Inversion	0.19%	0.03%	6.33
Aspiration	0.17%	0.08%	2.13
Rash Papular	0.17%	0.08%	2.13
Tachypnoea	0.17%	0.07%	2.43

Abbreviation: NOS = not otherwise specified.

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Earl Hearst
5/21/03 11:08:23 AM
MEDICAL OFFICER

Thomas Laughren
7/1/03 10:40:33 AM
MEDICAL OFFICER
I agree that this supplement is approvable; see memo
to file for more detailed comments.--TPL

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 1, 2003

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Zyprexa (olanzapine) as adjunctive therapy for the treatment of manic or mixed episodes in bipolar disorder

TO: File NDA 20-592/S-018
[Note: This overview should be filed with the 9-17-02 submission of this supplement.

1.0 BACKGROUND

Zyprexa (olanzapine) is a 5HT₂/D₂ antagonist that was approved for the "management of the manifestations of psychotic disorders" on 9-30-96. It was also approved for "the short-term treatment of acute manic episodes associated with Bipolar I Disorder" on 3-17-00. Supplement 018 includes data in support of a claim for Zyprexa as adjunctive therapy for the short-term treatment of manic or mixed episodes in bipolar disorder, in a dose range of 5-20 mg/day.

It should be noted that, at the current time, there are 3 drugs specifically approved for the treatment of mania, i.e., lithium, Depakote (valproate), and Zyprexa (only as monotherapy). While Depakote and Zyprexa are approved only for short-term use in treating mania, lithium is approved for both acute treatment and for maintenance treatment of mania. A fourth drug, Lamictal, has also been approved for maintenance treatment in bipolar disorder, but not for acute treatment.

We had several discussions with the sponsor regarding the development program for Zyprexa as adjunctive therapy in the short-term treatment of mania (i.e., 2 identical studies under 1 protocol, HGFU), including (1) a phone conversation on 2-20-97, (2) a 6-24-97 preNDA meeting for the monotherapy supplement, (3) a 2-23-00 meeting during which we informed the sponsor that, given the fact that Zyprexa was already approved as monotherapy for acute mania, a single positive adjunctive therapy trial for Zyprexa in mania would suffice to support the adjunctive therapy claim, and (4) a 5-30-02 formal PreNDA meeting at which time we discussed with the sponsor the planned adjunctive therapy in mania supplement. We reached agreement on what were mostly formatting issues regarding this supplement at that meeting.

Since the proposal is to use the currently approved Zyprexa formulations for this expanded population, there was no need for chemistry or pharmacology reviews of this supplement. Drug interaction data for (1) olanzapine and lithium, and (2) olanzapine and valproate (both in vivo) were submitted as part of this supplement, and were reviewed by Veneeta Tandon, Ph.D. from the biopharmaceutics group. The primary review of the clinical efficacy and safety data was done by Earl Hearst, M.D. from the clinical group. Ohidul Siddiqui, Ph.D., from the Division of Biometrics, reviewed the efficacy data for the HGFU studies.

The original supplement for this expanded indication (S-018) was submitted 9-17-02. There was no safety update.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

As Zyprexa is a marketed product, there were no chemistry issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Zyprexa is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As noted, drug interaction data for (1) olanzapine and lithium (from in vivo study E001, submitted with the original NDA, on 9-21-95), and (2) olanzapine and valproate (from in vivo study HGGB, submitted for the first time with this supplement) were submitted as part of this supplement, and were reviewed by Veneeta Tandon, Ph.D. from the biopharmaceutics group. The lithium study revealed that olanzapine did not influence the kinetics of lithium. The valproate study revealed that olanzapine did not influence the kinetics of valproate. OCPB found the drug interaction labeling language proposed by the sponsor to be acceptable.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Data were submitted from 2 identically designed, placebo-controlled, 6-week adjunctive therapy trials under protocol HGFU, and these data were the focus of our review. It should be noted that a randomized withdrawal study for responders on either olanzapine or placebo in these studies followed the acute phase, and these data are the basis for a separate supplement submitted in support of adjunctive maintenance efficacy.

5.1.2 Summary of 2 HGFU Studies

As noted, 2 identical studies (studies 1 & 2) were conducted under this protocol. There were a total of 40 investigators at a total of 42 US and Canadian sites. The sites were randomly assigned to study 1 or 2 prior to any patient enrollment. These were randomized, double-blind, parallel group 6-week studies in patients with DSM-IV diagnoses of manic or mixed episodes, with or without psychotic features, associated with bipolar I disorder. All patients were being maintained on either valproate (50 to 125 mg/mL) or lithium (0.6 to 1.2 mEq/L), and experienced the manic or mixed episodes despite such maintenance therapy. Patients (n=175 for study 1 and n=169 for study 2) were assigned to either olanzapine (initiated at a dose of 10 mg/day, and then titrated in a range of 5-20 mg/day) or placebo (dosing with olanzapine or matching placebo was in the evening). The randomization was 2:1, olanzapine:placebo. Patients were continued on whatever mood stabilizer they had been on at the time of entry, in the same plasma level ranges as indicated above. Treatment was initiated on either an inpatient or outpatient basis. Patients were roughly half males, predominantly white, and the mean age was about 40 years.

The primary outcome was change from baseline in the Young Mania Rating Scale (YMRS) total score, an 11-item scale including items related to both manic and psychotic behavior. Patients were also assessed on the following: PANSS; HAMD-21; and CGI.

I will focus my comments on mean change from baseline in the YMRS total score, since this was identified by protocol as the primary outcome. Our review focused on an intent-to-treat sample that included all patients randomized for whom efficacy assessments were available at baseline and at least one followup time (apparently regardless of whether or not they received assigned treatment). The statistical model that our statistical reviewer used for YMRS change from baseline was ANCOVA (LOCF)[using baseline YMRS as covariate], including only treatment and investigator terms. It should be noted that the protocol specified primary analysis was ANOVA, without covariate adjustment, and using treatment, investigator, and treatment-by-investigator terms in the model, even though the interaction term was not significant. While study 1 technically failed using this model (p=0.051) and study 2 was positive (p=0.025), I am inclined to accept the statistical reviewer's analysis, since this is what is ordinarily done and is more appropriate for these data. Thus, I will present only the statistical reviewer's results.

Study 1 Results

77% completed through 6 weeks on placebo vs 73% on olanzapine. The median olanzapine dose for completers was 10 mg.

The overall analysis for YMRS was significant (p=0.002):

Efficacy Results on YMRS Total Score for Study 1 (LOCF)

	Baseline YMRS	Obaseline YMRS	[P-value(vs pbo)]
Olz+MS (n=119)	22	-13	0.002
Placebo (n=56)	22	-9	

While not described here, results on the OC analysis also favored olanzapine over placebo. Analyses of secondary outcomes also favored olanzapine over placebo.

An additional analysis was conducted for this study, excluding data for investigator 21 (n=8), since this investigator was discontinued due to noncompliance with good clinical practices. The study remained positive.

Study 2 Results

66% completed through 6 weeks on placebo vs 66% on olanzapine. The median olanzapine dose for completers was 10 mg.

The overall analysis for YMRS was significant (p=0.001):

Efficacy Results on YMRS Total Score for Study 2 (LOCF)

	Baseline YMRS	Obaseline YMRS	[P-value(vs pbo)]
Olz+MS (n=110)	22	-13	0.001
Placebo (n=59)	23	-9	

While not described here, results on the OC analysis also favored olanzapine over placebo. Analyses of secondary outcomes also favored olanzapine over placebo.

Pooled analysis on the YMRS based on subgroups for age, gender, and ethnic origin revealed no interactions for these strata.

Comment: Both Drs. Hearst and Siddiqui considered these positive studies, and I agree.

5.1.3 Conclusions Regarding Efficacy Data

Thus, these 2 trials support the effectiveness of adjunctive olanzapine therapy in bipolar I patients with emergent manic or mixed episodes occurring despite maintenance treatment with either valproate or lithium. Although technically only 1 of the 2 studies was positive relying on the protocol specified analysis, I am inclined to consider Dr. Siddiqui's analysis the more definitive analysis. In any case, only 1 positive study would have been sufficient to support this claim, given the fact that olanzapine monotherapy is already approved for this indication. It should be noted that we are currently reviewing data for adjunctive maintenance treatment with olanzapine for this same population.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data for Zyprexa as adjunctive therapy in the treatment of mania, derived from studies done under the protocol for HGFU, as well as from postmarketing data and a literature review, were reviewed by Dr. Hearst. There were a total of n=344 patients randomized for studies 1 and 2 (n=229 for olanzapine and n=115 for placebo). Safety data were included both for the acute phase and also for n=136 patients from the acute phase who entered the 18-month extension phase. Only n=31 had completed this phase as of the 11-30-00 cutoff date.

In addition to this clinical trials experience, the sponsor summarized spontaneously reported adverse events in patients receiving adjunctive olanzapine (i.e., added on to another mood stabilizer). They also summarized any pertinent published literature.

Overview of Safety Findings

Overall, the profile of adverse events, labs, vital sign, and ECGs observed in this small sample of patients was not obviously different from that seen in the original NDA population, and there were no new, unrecognized serious adverse events that could be considered related to olanzapine use. Similarly, a review of spontaneous reports and pertinent published literature in patients being treated with olanzapine as add-on therapy for bipolar disorder did not reveal any signal of serious events occurring in this subpopulation. Nevertheless, there were drug-related adverse events resulting from the addition of olanzapine to existing mood stabilizer therapy, and 3 events stood out as being related to discontinuation following the addition of olanzapine: weight gain, somnolence, and peripheral edema. Our proposed labeling will reflect these excess risks.

5.3 Clinical Sections of Labeling

We have made only minor changes to the sponsor's proposed additions to labeling based on this supplement.

6.0 WORLD LITERATURE

Dr. Hearst examined the published literature for Zyprexa included in the NDA and did not discover any previously unrecognized important safety concerns for this drug.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Zyprexa is not approved as adjunctive therapy for the treatment of mania anywhere at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 US sites: Logue and Weisler. The Logue site was classified as NAI and the Weisler site was classified as VAI, based on minor deficiencies. Overall, the data from these 2 sites were judged to be acceptable.

10.0 APPROVABLE LETTER

An approvable letter acknowledging our decision to proceed with an approval action pending agreement on labeling has been included with the approvable package.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has now submitted sufficient data to support the conclusion that olanzapine is effective and acceptably safe as adjunctive therapy in the acute treatment of mania. I recommend that we issue the attached approvable letter with our proposed labeling for this product.

**Appears This Way
On Original**

cc:

Orig NDA 20-592/S-006 (Zyprexa/Mania)

HFD-120/Division File

HFD-120/TLaughren/RKatz/EHearst/DBates

DOC: MEMZYPMN.AE1

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Laughren
7/1/03 11:17:12 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

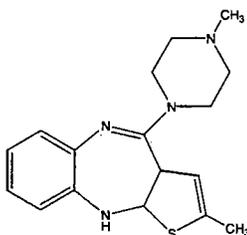
NDA 20-592/S-018

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF SUPPLEMENT

1. ORGANIZATION: HFD-120
2. NDA 20-592
3. SUPPLEMENT NUMBER AND DATES: SE1-018
LETTER DATE: 09-16-02
STAMP DATE: 09-17-02
4. AMENDMENT/REPORTS/DATES:
LETTER DATE: 09-26-02
LETTER DATE: 11-13-02
5. RECEIVED BY CHEMIST: 09-17-02

6. APPLICANT NAME & ADDRESS: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
7. NAME OF DRUG: Zyprexa[®] Tablets
8. NONPROPRIETARY NAME: Olanzapine
9. CHEMICAL NAME and STRUCTURE: 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine



10. DOSAGE FORMS: Tablets
11. POTENCY: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg
12. PHARMACOLOGICAL CATEGORY: antipsychotic
13. HOW DISPENSED: (Rx) (OTC)
14. RECORD and REPORTS CURRENT: Yes No
15. RELATED IND/NDA/DMF: n/a

16. SUPPLEMENT PROVIDES FOR: This supplement provides for the use of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder.

17. ADDITIONAL COMMENTS: The applicant indicates that all relevant CMC information is provided in NDA 20-592. All Chemistry manufacturing and control information pertaining to the drug substance and the drug product remain unchanged.

18. CONCLUSIONS & RECOMMENDATIONS:

The applicant has provided adequate information to support this change. From a CMC perspective, it is recommended that this supplement be APPROVED.

cc: NDA 20-592 Division file
TOliver
SMclamore
DBates

Review Notes:

1. DRUG SUBSTANCE

The applicant references NDA 20-592 for all relevant CMC information.

Evaluation: Adequate

NDA 20-592 was approved September 30, 1996. The applicant has not identified any additional changes to the drug substance portion of this application.

2. DRUG PRODUCT

The applicant references NDA 20-592 for all relevant CMC information.

Evaluation: Adequate

NDA 20-592 was approved September 30, 1996. The applicant has not identified any additional changes to the drug product portion of this application.

3. PACKAGE INSERT AND LABELING

Evaluation: Adequate

The package insert was reviewed and there were no changes to the Description or to the How Supplied Section of the package insert.

4. ENVIRONMENTAL ASSESSMENT

In the September 26, 2002 amendment, the applicant requested a categorical exclusion for the environmental assessment however the applicant did not provide a specific citation from the CFR. The applicant was telephoned on November 12, 2002 and asked to provide a CFR reference as indicated in 21CFR 25.15 (d) as well as a statement indicating that there are no known extraordinary circumstances that will adversely effect the environment. The applicant responded via fax on November 13, 2002 and indicated that the firm was requesting categorical exclusion under 21 CFR 25.31 (a).

Evaluation: Adequate

Based on 21 CFR 25.31(a), a categorical exclusion should be granted as the action taken in this supplement does not increase the use of the active moiety.

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sherita McLamore,
11/19/02 10:44:36 AM
CHEMIST

Thomas Oliver
11/19/02 11:09:25 AM
CHEMIST

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ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-018

STATISTICAL REVIEW(S)



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

STATISTICAL REVIEW AND EVALUATION

NDA: 20-592 (REF# SE1-018)
DRUG NAME: Zyprexa (olanzapine) Tablets
INDICATION: Bipolar 1 Disorder
SPONSOR: Eli Lilly and Company
STATISTICAL REVIEWER: Ohidul Siddiqui
DATE OF DOCUMENT: September 17, 2002

DISTRIBUTION:

HFD-120 Doris Bates, Ph.D. Project Manager
Paul Andreason, M.D., Clinical Reviewer
Thomas Laughren, M.D., Team Leader
Russell Katz, M.D., Director
HFD-710 Kun Jin, Ph.D., Team Leader
George Chi, Ph.D., Director
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EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

The sponsor submitted results of two adequate and well-controlled clinical trials to support the efficacy of olanzapine compared with placebo when each was added to the patient's current mood stabilizer therapy to assess acute olanzapine therapy for the treatment of bipolar I disorder. Based on the primary efficacy analyses (LOCF comparison of mean change from baseline to endpoint in Y-MRS total score) in each of the two studies, the superiority of olanzapine plus current mood stabilizer therapy (Olz+MS) over placebo plus current mood stabilizer therapy (Pla+MS) was indicated by a statistically significant difference between the treatment groups in the decrease in Y-MRS total score at endpoint. These results demonstrated that olanzapine in the dose range 5-20 mg/day added to mood stabilizer therapy for the treatment of acute manic or mixed bipolar episodes, with or without psychotic features, was effective over the 6-week acute phase.

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ON ORIGINAL

INTRODUCTION

The sponsor designed the Study F1D-MC-HGFU to evaluate the efficacy of olanzapine compared with placebo when each was added to the patient's current mood stabilizer therapy to assess acute olanzapine therapy for the treatment of bipolar I disorder. The Study F1D-MC-HGFU was designed as 2 randomized, double-blind, parallel studies of approximately 168 inpatients or outpatients per study (yielding a total of 336 patients overall) meeting diagnostic criteria for bipolar I disorder, manic or mixed, with or without psychotic features, according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Patient Version (SCID-P). The study was conducted at 42 investigative sites within the United States and Canada. Investigative sites were divided into 2 separate studies at random prior to any patient enrollment.

In each of the two studies, the efficacy of acute therapy was evaluated using improvement in clinical symptomatology after up to 6 weeks of double-blind therapy as measured by reductions from baseline in the Young-Mania Rating Scale (Y-MRS) total score.

Qualified patients from Study Period I (screening and washout) were assigned by random allocation at Visit 2 to one of two treatment groups: olanzapine in a dose range of 5-20 mg/day added to current mood stabilizer therapy (Olz+MS) or placebo added to current mood stabilizer therapy (Pla+MS). Randomization was performed at a 2:1 ratio. Study Period II was a 6-week double-blind therapy period. Patients who showed adequate response at the end of Study Period II (Visit 8) entered Study Period III.

The sponsor has not stated any claim based on the Study period III data. Therefore, there will be no statistical review on the Study period III data. The study design is illustrated in Figure 1.

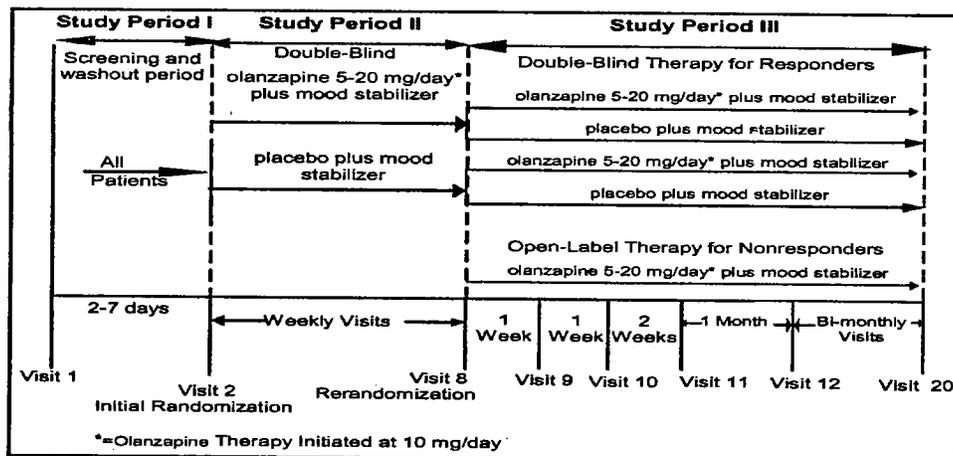


Figure 1. Illustration of Study Design F1D-MC-HGFU

Patients, ages 18-70 years, must have an initial total score (at Visits 1 and 2) on the Young-Mania Rating Scale (Y-MRS) of at least 16; a diagnosis of bipolar I disorder displaying an acute manic or mixed episode (with or without psychotic features), according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as determined by the SCID-P; and at least 2 previous depressed, manic, or mixed episodes associated with bipolar I disorder. Patients must have documented trials of lithium or divalproex sodium/valproic acid alone for at least 2 weeks immediately prior to Visit 1, with minimum blood levels of 0.6 mEq/l for lithium and 50 µg/mL for valproate.

Study Period I was the screening and washout period of the study. At Visit 1, patients must have met all inclusion and exclusion criteria specified in the protocol. Study Period II was the 6-week, acute, double-blind therapy period of the study. Patients were assessed weekly from Visit 2 through Visit 8. During Study Period II, the dose of mood stabilizer should remain within the therapeutic range. The therapeutic range for lithium was 0.6 mEq/l to 1.2 mEq/l, and 50 µg/mL to 125 µg/mL for valproate.

All patients began Study Period II (Visit 2) with either olanzapine 10 mg (2 tablets of 5 mg) or placebo (2 tablets) given once per day in the evening, in addition to the mood stabilizer therapy they were taking upon entry into the study (lithium or valproate). For all patients in Study Period II: following 1 day on 2 tablets/day, the daily dose was adjusted upward, as clinically indicated, by one 5 mg increment/day (1 tablet) within the allowed dose range of 5 to 20 mg/day. Decreases in dosages occurred at any time, by any number of decrements, to a minimum of 1 tablet per day. Patients not able to tolerate the minimum dosage of study medication (1 tablet/day) were discontinued from the study.

Efficacy Analyses

Change from baseline to endpoint in the Y-MRS total score was the primary efficacy measure in Study Period II. Secondary efficacy assessments included the PANSS (total, positive, and negative), the HAM-D-21 total, and the CGI-BP Severity scores.

The null hypothesis of principal interest was that Olz+MS was equal to Pla+MS therapy in terms of last observation carried forward (LOCF) mean change in Y-MRS total score after up to 6 weeks of double-blind olanzapine therapy (Study Period II). Analysis of variance (ANOVA) models were used to evaluate continuous data; the models generally included the terms for treatment, investigator, and treatment-by-investigator interaction. If there was less than 2 patients per treatment group within an investigative site, those data were pooled with data from other small investigative sites. All tests of hypotheses were tested at a 2-sided α level of 0.05. Treatment-by-investigator was tested at an α level of 0.10.

Primary analyses were done on an intent-to-treat basis. When LOCF mean change from baseline to endpoint was assessed, patients were included in the analysis only if a patient had a baseline and a post baseline measure. For the analysis of Study Period II, unless otherwise defined, a baseline measure was the Visit 2 observation; if it was missing, then

the baseline measure was the Visit 1 observation. A patient's endpoint measure was defined as his/her last measure in the appropriate study period. All total scores from rating scales and subscales were derived from individual items. If any of the individual items were missing, the total score was treated as missing.

An observed and LOCF visitwise analyses of Y-MRS total score were performed for Study Period II.

Subgroup Analyses

Subgroup analyses of the primary efficacy rating measure Y-MRS were performed for origin, gender, and age if there were at least 10 patients in each treatment group. In the analyses, Y-MRS measure was assessed using ANCOVA models, including the terms for treatment, investigator, subgroup, and the treatment-by-subgroup interaction. The treatment-by-subgroup interaction was tested to determine whether treatment differences in the outcome measure were the same for each subgroup category.

Interim Analyses

No interim analyses were planned for this study.

Table 1: Patients baseline characteristics by treatment groups of each of the two studies (ITT Population).

Study No.	Treatment Group (N)	% Male	Race (% of White)	Mean Age (years)	Baseline Mean Y-MRS total score
Study 1	Olz+MS (N=119)	36.1%	82.4%	39.6	22.3
	Pla+MS (N=56)	50.0%	83.9%	40.2	22.1
Study 2	Olz+MS (N=110)	52.7%	89.1%	41.9	22.4
	Pla+MS (N=59)	61.0%	84.7%	40.6	23.2

Table 2. Percentages of withdrawn patients in the acute phase by reason (ITT population).

	Study 1		Study 2	
	Olz+MS (N=119)	Pla+MS (N=56)	Olz+MS (N=110)	Pla+MS (N=59)
Randomized ITT (N)	119	56	110	59
Total Completers (%)	73.1%	76.8%	66.4%	66.1%
Total Withdrawn (%)	26.9%	23.2%	33.6%	33.9%
Adverse event (%)	9.2%	3.6%	12.7%	-
Lack of Efficacy (%)	1.7%	8.9%	4.5%	15.3%
Lost to follow-up (%)	3.4%	1.8%	0.9%	3.4%
Patient Decision (%)	3.4%	1.8%	8.2%	1.7%
Criteria not met (%)	8.4%	3.6%	1.8%	5.1%
Physician Decision (%)	0.8%	3.6%	3.6%	6.8%
Satisfactory Response (%)	-	-	0.9%	-
Sponsor Decision	-	-	0.9%	1.7%

Table 3. Percentages of subjects remained in each Visit (ITT Population).

Study #	Treatment group (N)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Study 1	Olz+MS (N=119)	94.1%	89.9%	84.0%	77.3%	73.9%	73.1%
	Pla+MS (N=56)	94.1%	94.6%	85.7%	80.4%	76.8%	76.8%
Study 2	Olz+MS (N=110)	89.1%	81.8%	74.5%	73.6%	68.2%	66.4%
	Pla+MS (N=59)	94.9%	86.4%	79.9%	76.3%	66.1%	66.1%

Table 4. LOCF and OC analyses on Y-MRS Total Score (ITT population) by Visit

Study #	L.S mean change from baseline in Y-MRS Total Score						
	Treatment group	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Study 1	LOCF Analysis						
	Olz+MS (N=119)	-7.18	-9.91	-10.42	-11.54	-12.81	-13.34
	Pla+MS (N=56)	-4.59	-7.23	-7.17	-9.45	-10.23	-9.27
	P-values:						
	Olz+MS vs. Pla+MS	.006	.022	.006	.072	.034	.002
	OC Analysis						
	Olz+MS (N=119)	-7.18	-10.49	-10.78	-12.39	-13.96	-14.74
	Pla+MS (N=56)	-4.59	-7.82	-7.76	-11.21	-12.76	-11.58
	P-values						
	Olz+MS vs. Pla+MS	.006	.022	.014	.327	.378	.038
Study 2	LOCF Analysis						
	Olz+MS (N=110)	-5.84	-7.35	-9.68	-9.64	-12.26	-13.20
	Pla+MS (N=59)	-4.69	-7.05	-8.41	-8.96	-8.54	-8.70
	P-values						
	Olz+MS vs. Pla+MS	.254	.795	.289	.591	.007	.001
	OC Analysis						
	Olz+MS (N=110)	-5.84	-7.47	-10.12	-10.52	-14.18	-15.45
	Pla+MS (N=59)	-4.69	-6.36	-8.70	-9.49	-9.06	-10.51
	P-values						
	Olz+MS vs. Pla+MS	.254	.339	.242	.449	<.001	.001

FINDINGS

Demographics and Other Baseline Characteristics

Table 1 summarizes the demographic characteristics of the ITT population by treatment groups. Within each study, the treatment groups were comparable at baseline with respect to mean age, ethnic origin and gender. There was no evidence of any treatment-group differences at baseline with respect to both the primary (Y-MRS total score) and secondary (PANSS total, positive, and negative scores; HAMD-21 total score; and CGI-BP Severity scores) efficacy parameters.

Number of Subjects Present at the study endpoint

Table 2 summarizes the disposition of the randomized patients and the reasons the patients discontinued from the acute phases of the two studies. In study #1, there was no difference in the proportion of patients who completed the acute phase of the study between the Olz+MS (73.1%) and Pla+MS (76.8%) treatment groups. However, the proportion of patients who discontinued from the acute phase of the study due to lack of efficacy was different between the Olz+MS treatment group (1.7%) and the Pla+MS treatment group (8.9%).

In study #2, there was no difference in the proportion of patients who completed the acute phase of the study between the Olz+MS (66.4%) and the Pla+MS (66.1%) treatment groups. There was, however, a greater proportion of patients who discontinued the acute phase of the study due to lack of efficacy in the Pla+MS treatment group (15.3%) than in the Olz+MS treatment group (4.5%). In addition, there was a greater proportion in the Olz+MS treatment group (12.7%) who discontinued due to adverse events than in the Pla+MS treatment group (0%). The percentages of patients remained at each visit are listed in Table 3. In both studies, the percentages are comparable at each visit between the two groups.

Primary Efficacy Results

Protocol specified statistical model to analyze the primary efficacy measure Y-MRS total scores was an Analysis of Variance (ANOVA) model; and the model included the terms for treatment, investigator, and treatment-by-investigator interaction. In both of the studies, the treatment-by-investigator interaction term was statistically insignificant ($p=0.421$, for study#1; $p=0.404$, for study#2). Although the interaction term was insignificant, the sponsor kept the term in the model in testing the least-square mean difference between the two treatment groups. Additionally, the sponsor did not include the baseline score of Y-MRS scale as a covariate in the model. It is a common practice in the Division of Neuropharmacological Drug Products (DNBP) to include baseline score as covariate in evaluating antipsychotic drug. Therefore, this reviewer reanalyzed the change from baseline to endpoint in Y-MRS total score using the ANCOVA model which included the terms treatment, investigator, and baseline score of Y-MRS (as a covariate), and tested the least-square mean difference between the two treatment groups.

Based on the protocol specified statistical analysis model on the primary efficacy measure the LOCF mean change from baseline to Visit 8 (Week 6 of therapy) in Y-MRS total scores, the Olz+MS treatment group experienced a greater mean change in Y-MRS total score, as compared to the Pla+MS treatment group in study #1. However the difference was not statistically significant ($p=0.051$). In study #2, the Olz+MS treatment group experienced a greater mean change in Y-MRS total score than the Pla+MS treatment group, and the mean difference was statistically significant ($p=0.025$). Based on the sponsor's findings, study#1 is a failed study and study#2 is a positive study.

Table 4 lists the LOCF and OC analyses on the change from baseline in Y-MRS total score. The analyses were conducted on the change from baseline to endpoint in Y-MRS

total score using the ANCOVA model, which included the terms treatment, investigator, and baseline score of Y-MRS (as a covariate). Finally, the statistical significance of least-square mean difference between the two treatment groups were tested. In both studies, the least square differences between the two groups were statistically significant ($p=.002$ (study#1); $p=.001$ (study#2)). That is, after dropping the insignificant treatment-by-investigator interaction term from the model and including baseline score of Y-MRS as a covariate in the model, both studies became positive studies. The Olz+MS treatment group showed significant efficacy for the treatment of bipolar 1 disorder, as compared to the Pla+MS treatment group. The results of the OC analyses were also similar to the results of the LOCF endpoint analyses.

For the study#1, an additional analysis of the change from baseline to endpoint for the Y-MRS total score was performed after excluding enrolled patients from Investigator 021. This additional analysis was performed because Investigator 021 was discontinued due to noncompliance with good clinical practices. A total of 8 patients were enrolled at this site, with 6 patients randomized to receive Olz+MS treatment group, and 2 patients randomized to receive Pla+MS treatment group. After excluding the eight patients enrolled at this site from the final analysis, study#1 remained a positive study with respect to its primary efficacy result.

Secondary Efficacy Results

In both studies, the Olz+MS treatment group had statistically significantly greater improvement than the Pla+MS treatment group in PANSS total; CGI-BP Severity of overall bipolar illness; CGI-BP Severity of depression; and HAMD-21 total scores based on both the sponsor's findings, as well as this reviewer's findings using the ANCOVA model which included the terms treatment, investigator, and baseline score as a covariate.

Subgroup Analysis Results

Subgroup analyses were performed to examine the consistency of treatment effects over the strata of demographic characteristics. The stratifying characteristics included in these analyses were age (<40 years, \geq 40 years), gender, ethnic origin (Caucasian, other). A subgroup was analyzed only if the number of patients in each stratum was 10 or more. For the primary measure Y-MRS total score, no statistically significant treatment-by-subgroup interactions were found for any of the above subgroups.

REVIEWER'S OVERALL CONCLUSION

Based on the primary efficacy analyses (LOCF comparison of mean change from baseline to endpoint in Y-MRS total score) in each of the two studies, the superiority of Olz+MS over Pla+MS was indicated by a statistically significant difference between the treatment groups in the decrease in Y-MRS total score at endpoint. These results demonstrate the superiority of olanzapine added to lithium or valproate over placebo added to lithium or valproate in the acute treatment of acute mania.

In conclusion, olanzapine in the dose range 5-20 mg/day added to mood stabilizer therapy for the treatment of acute manic or mixed bipolar episodes, with or without psychotic features, was effective over the 6-week acute phase.

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Ohidul Siddiqui
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George Chi
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-018

**CLINICAL PHARMACOLOGY/
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name): Olanzapine

PRODUCT (Brand Name): ZYPREXA

DOSAGE FORM: Tablets

DOSAGE STRENGTHS: 2.5, 5, 7.5, 10, 15 and 20 mg

NDA: 20-592 (SE1-018 and 019)

NDA TYPE: 6S

INDICATION: SE1-018: Zyprexa in combination with lithium and valproate for the treatment of manic episodes associated with Bipolar I disorder
SE1-019: Long-term treatment of bipolar I disorder

SUBMISSION DATE: 9/16/02, 11/20/02

SPONSOR: Eli Lilly and Company

REVIEWER: Veneeta Tandon, Ph.D.

TEAM LEADER: Ramana Uppoor, Ph.D.

OCPB DIVISION: DPE I, HFD 860

OND DIVISION: HFD 120

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EXECUTIVE SUMMARY

The objective of NDA 20-592 (SE1- 018) is to gain approval for the use of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder. NDA 20-592 (SE1- 019) is submitted to gain approval for the use of Zyprexa for the long term treatment of bipolar I disorder.

The efficacy of ZYPREXA in combination with lithium or valproate was established in two randomized, double-blind placebo-controlled studies in patients with acute manic or mixed episode with or without psychotic features (Protocol F1D-MC-HGFU: Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder). Olanzapine doses studied were 5, 10, 15 and 20 mg/day given once a day for 6 weeks.

A drug interaction study was also conducted to assess the effect of olanzapine on steady state valproate levels (Protocol F1F-LC-HGGB: Olanzapine- Divalproex sodium interaction trial).

The results showed that in vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. The effect of valproate on olanzapine pharmacokinetics could not be determined robustly from this study.

The information on Lithium interaction with olanzapine has been taken from Study E001; submitted September 21, 1995 with NDA 20-592. The results indicated that there was no interaction between olanzapine and lithium.

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RECOMMENDATION

NDA 20-592 (018 and 019) are acceptable from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics. The sponsor's labeling changes in the Drug Interaction section under PRECAUTIONS are acceptable and should apply to both SE1-018 and SE1-019.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D. _____

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LABELING RECOMMENDATION

The following Labeling changes made by the sponsor in the Drug interaction Section under PRECAUTIONS are acceptable and should apply to both supplements 018 as well as 019. The original valproate section has been deleted and a new section has been added. Lithium has been given its own sub heading and has been removed from a list of general drugs that did not show interaction.

Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.

Valproate — Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. In vivo administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

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Study FID-LC-HGGB: *Olanzapine-Divalproex sodium/valproic acid interaction trial*

The objectives of the study were:

Part A: To determine any pharmacokinetic or pharmacodynamic drug interaction, safety, to assess effects of single and multiple doses of olanzapine on steady-state valproic acid concentrations; and to evaluate neuroendocrine effects during coadministration of divalproex sodium (hereafter designated as divalproex) and olanzapine.

Part B: To determine any pharmacokinetic drug interaction during coadministration of divalproex/valproic acid and olanzapine, to determine effects of multiple-dose divalproex on olanzapine concentration profiles, and to assess the effects of multiple doses of olanzapine on steady-state valproic acid concentrations.

The study design is as follows:

Study Design	<p><u>Part A</u> was designed as a parallel comparison of olanzapine versus placebo coadministered with divalproex.</p> <p><u>Part B</u> was designed for competitive enrollment with Part A and was a parallel comparison of olanzapine versus placebo coadministered with divalproex from patients with bipolar illness obtained from Study FID-MC-HGFU (only 1 patient enrolled in this part)</p>
Study Population	<p>N=42 patients with bipolar or schizoaffective disorder stabilized on divalproex (blood levels of valproic acid: 50-125 µg/mL) for 2 months and possibly on stable dose of lithium (minimum blood levels of 0.6 mEq/L).</p> <p>Patients could also be entered into the trial if they were stabilized for at least 2 months on one of the following: bupropion (up to a 300-mg daily dose) or an SSRI antidepressant (other than fluvoxamine).</p> <p>27 out of 42 subjects completed the trial.</p> <p><u>Gender:</u> 20M & 22F, <u>Ages:</u> 18-65 yrs <u>Weight:</u> 54.1-151 kg <u>Race:</u> 2 Black, 1 Hispanic, 1 Other, 38 Caucasian</p>
Treatment Group	<p>A: Olanzapine/daily divalproex (Stabilized on divalproex) B: Placebo/ daily divalproex (Stabilized on divalproex)</p>
Dosage and Administration	<p>A: <u>Olanzapine:</u> 10 mg as a single dose and then as a multiple dose regimen of 10 mg once daily for approximately 2 weeks A 6 days washout between single and multiple dose regimen 10 mg tablets (CT04017, CT10117, CT11817)</p> <p>B: <u>Placebo</u> (CT08802, CT08960, CT10215)</p> <p><u>Divalproex:</u> An individualized dosage (500 to 2250 mg per day) which maintained valproic acid plasma concentrations within the</p>

	<p>therapeutic range (50-125 µg/mL). Supplied as 125-mg, 250-mg, 500-mg, 750-mg, 1000-mg, or 1500-mg delayed-release tablets from various manufacturer's lot numbers. Administered once or twice daily.</p> <p>Daily regimen maintained throughout the study.</p> <p><u>Diet:</u> On the day indicated for pharmacokinetic studies, patients ate a regular diet in the evening and could take olanzapine (or placebo) plus divalproex with a snack approximately 2.5 hours before bedtime. On these occasions, patients were asked to remain upright for approximately 2 hours after dosing.</p>									
Sampling: Blood	<p><u>For Olanzapine/metabolites:</u> For single dose part: At Day 1: At 0,1,2,4,6,8,10,12,24,36,48,72,96, and 120 hours postdose. For multiple dose part: At the end of Week 1(Day 13): At 0, 2,4,8,12, and 24 hours At the end of Week 2 (Day 20): At 0, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, and 120 hours postdose</p> <p><u>For Valproic acid:</u> At Days (-14), (-1), 1, 13, and 20: 12 hours before and 12 hours after the evening drug administration. Samples were obtained before the morning drug doses if the patient was on a twice-daily dosing schedule. At Days (-1), 13 and at discharge: for therapeutic concentrations</p>									
Urine	<p><u>For Valproic acid/metabolites:</u> 12 hour urine on Days (-14), (-1), 13, and 20 for valproic acid and metabolite ratios.</p>									
Feces	<p>none</p>									
Analysis	<p>HPLC for olanzapine in plasma GC for valproic acid in plasma and urine</p> <p>Lower Limits of Quantitation</p> <table border="1"> <thead> <tr> <th></th> <th>Plasma</th> <th>Urine</th> </tr> </thead> <tbody> <tr> <td>Olanzapine</td> <td>0.25 ng/mL</td> <td></td> </tr> <tr> <td>Valproic Acid</td> <td>10 mcg/mL</td> <td>40 mcg/mL</td> </tr> </tbody> </table> <p>Assay validation complete and acceptable (see Page 20)</p>		Plasma	Urine	Olanzapine	0.25 ng/mL		Valproic Acid	10 mcg/mL	40 mcg/mL
	Plasma	Urine								
Olanzapine	0.25 ng/mL									
Valproic Acid	10 mcg/mL	40 mcg/mL								
PK Assessment	<p>Plasma concentrations of valproic acid and olanzapine were used to assess the potential effects of each drug upon the other. Excretion of valproic acid in urine was assessed. C_{max}, t_{1/2}, CL and V_d of olanzapine and metabolites</p>									
PD Assessment	<p>CGI-BP and alertness assessments were evaluated during olanzapine-divalproex coadministration and compared with assessments during placebo-divalproex.</p>									
Safety	<p>Comparisons between treatment groups for the QTc and prolactin values were performed during the olanzapine-divalproex treatment group versus the placebo-divalproex group. Liver tests were evaluated for evidence of clinically significant liver injury.</p>									

Patient Disposition

27 out of 42 patients completed the study according to the protocol. A total of 12 patients excluded from the trial were attributed to unstable therapeutic levels of valproic acid during the 14 day evaluation period to assess the stability of therapeutic valproic acid concentrations. Other reasons were exclusionary laboratory results at entry or failure to meet other entry criteria. These patients signed the informed consent but did not receive any study drug.

The following Table shows the disposition of subjects in the study

Table: Accounting of Patients in Pharmacodynamic and Local Laboratory Valproic Acid Plasma Concentration Data Statistical Analyses

Treatment	Patient ID	Total
Placebo Group	1001, 2414, 2594, 3014, 3031	15
	3191, 3353, 5003, 5010, 5011	
	5012, 5018, 5019, 6002, 6003	
Olanzapine Group	2419, 2493, 2535, 2586 ^a , 2595	12
	2634, 5001, 5008, 5013, 5016	
	6001 ^a , 6006	
Sub Total		27
Part B	3053 ^b	1
Placebo Group		
Not Assigned to Treatment ^c	2632, 2637, 5002, 5004, 5005,	12
	5006, 5007, 5009, 5014, 5015,	
	6004, 6005	
Dropouts with Partial Data Not Included in Statistical Assessment	Placebo Group 2001 ^d Olanzapine Group 5017 ^d	1 1
Grand Total		42

^a Dropouts with partial data included in the analysis under ITT.

^b Local lab valproic acid concentrations used in statistical assessment.

^c Discharged before study drug administered. No analysis performed.

^d Not included in statistical assessment based because of minimal data (< 3 doses of study drug).

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Patients included in the final pharmacokinetic analysis are given in the following Table:

Table: Patients included in the final pharmacokinetic analysis

Patient Number	Treatment Group Assignment			PK of Plasma Olanzapine by Dose			PK of Plasma Valproic Acid by Treatment			PK of Urine Valproic Acid by Treatment		
	A	B	N/A	1 st	8 th	15 th	A	B	N/A	A	B	N/A
1001		X						X			X	
2001		X						X			P	
2414		X						X			X	
2419	X			X	X	X	X				X	
2493	X			X	X	X	X					
2535	X			X	X	X	X				X	
2586	X			P	P						P	
2594		X						X			X	
2595	X			X	X	X	X				X	
2632			X						N			P
2634	X			X	X	X					X	
2637			X						N			N
3014		X						X			X	
3031		X						X			X ^a	
3191		X						X			X	
3353		X						X			X	
5001	X			X	X	X	X				X	
5002			X						P			P
5003		X						X			X	
5004			X						P			P
5005			X						P			P
5008	X			X	X	X	X				X	
5010		X						X			X ^a	
5011		X						X			BD	
5012		X						X			X	
5013	X			X	X	X	X				X	
5016	X			X	X	X	X				X	
5017	X			P			X				P	
5018		X						X			X	
5019		X						X			X	
6001	X			P			P				P	
6002		X									X	
6003		X									X	
6004			X									N
6006	X			X	X	X					X ^a	
3053		X									N	
2001A		X						X			P	
5001A	X						P				P	
Total	14	18	6	13	11	10	9	15			10	14
Overall		38			10			24				24

Abbreviations: X = data analyzed, P = partial data (not included in group), N = no data, BD = below detection.

^a Urine data for these patients not included in percentage of dose excreted in urine calculation.

Pharmacokinetic Results:

Olanzapine and Olanzapine metabolites:

Plasma samples obtained during this study were analyzed for olanzapine and olanzapine after [] of the sample. The difference in these two measurements provides the plasma concentration of olanzapine glucuronide.

Mean±SD pharmacokinetic parameters for the olanzapine and its metabolite is given in the following Tables. For measurement of olanzapine glucuronide metabolite, the plasma samples were subjected to [] Measurement of [] sample reflects the summation of the concentrations of olanzapine plus its glucuronide conjugates. After subtraction of the olanzapine plasma concentration values from the measured concentration after [] the resulting difference is considered to be a calculated result reflecting the concentration of olanzapine glucuronide.

Table: Mean Olanzapine Pharmacokinetic Characteristics

Olanzapine Pharmacokinetics for olanzapine dose given with divalproex N = 10 Patients ^a	Mean (Range) C _{max} (ng/mL)	Mean (Range) Half-Life (hr)	Mean (Range) Clearance (L/hr)	Mean (Range) Volume of Distribution (L/kg)
Single Dose	9.28±3.29 (4.5 to 16.8)	37.8±7.94 (24.7 to 52.4)	26.7±12 (17.3 to 56.9)	14.3±3.8 (8.8 to 22.4)
8 th Multiple Dose	21.9±7.48 (10.8 to 38.1)	n.a.	27.8±10.3 (16.0 to 50.3)	n.a.
14 th or 15 th Multiple Dose	25.3±8.54 (11.4 to 41.4)	38.7±11.6 ^b (24.9 to 63.5)	24.9±9.23 (14.9 to 42.7)	13.2±2.92 ^b (10.3 to 18.1)

^a N = Number of patients who completed the trial and had a full profile of olanzapine pharmacokinetics.

n.a. not available (could not be estimated).

^b N = 9

Table: Mean Olanzapine [] Pharmacokinetic Characteristics

Olanzapine [] Pharmacokinetics for olanzapine dose given with divalproex N = 10 Patients ^a	Mean (Range) C _{max} (ng/mL)	Mean (Range) Half-Life (hr)	Mean (Range) Clearance (L/hr)	Mean (Range) Volume of Distribution (L/kg)
Single Dose	14.6±4.30 (8.75 to 22.9)	37.7±9.11 (22.9 to 54.6)	18.7±7.39 (11.6 to 37.6)	10.0±2.46 (5.2 to 14.6)
8 th Multiple Dose	30.9±8.37 (18.5 to 44.8)	n.a.	19.8±7.37 (11.3 to 35.8)	n.a.

14 th or 15 th Multiple Dose	34.2±10.9 (14.5 to 56.2)	39.5±9.69 ^b (26.4 to 55.6)	19.2±8.09 (11.2 to 38.6)	10.4±3.36 ^b (5.4 to 17.6)
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^aN = Number of patients who completed the trial and had a full profile of olanzapine pharmacokinetics.

n.a. not available (could not be estimated).

^bN = 9

Table: Mean Olanzapine Glucuronide Pharmacokinetic Characteristics

Olanzapine Glucuronide Pharmacokinetics for olanzapine dose given with divalproex N = 10 Patients ^a	Mean (Range) C _{max} (ng/mL)	Mean (Range) Half-Life (hr)	Mean (Range) Clearance (L/hr)	Mean (Range) Volume of Distribution (L/kg)
Single Dose	6.20±2.89 (2.3 to 12.7)	46.7±32.2 (13.8 to 107)	69.7±41.1 (24.8 to 162)	39.9±20.4 (13.0 to 66.7)
8 th Multiple Dose	11.2±6 (5.3 to 22.1)	n.a.	75.6±36.3 (24.0 to 125)	n.a.
14 th or 15 th Multiple Dose	10.6±6.05 (4.5 to 21.2)	52.0±23 ^b (23.3 to 88.5)	113±92.9 ^b (25.3 to 299)	88.9±115 ^b (11.2 to 387)

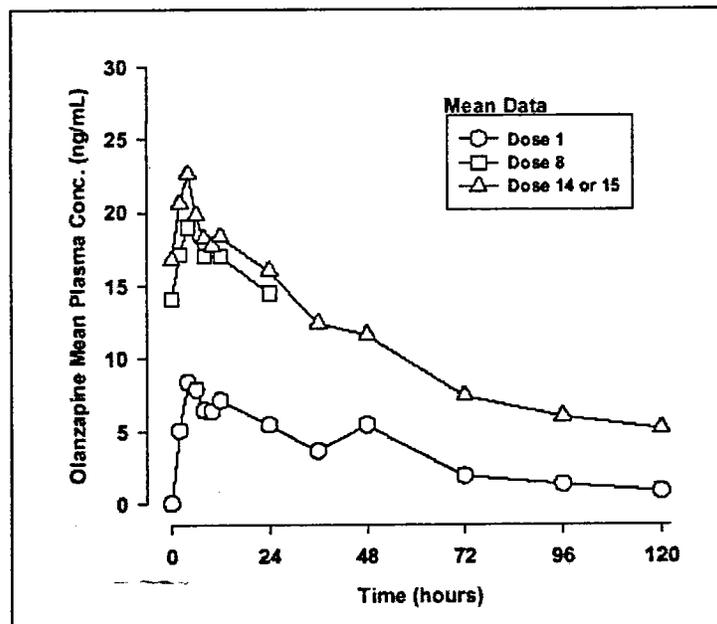
^aN = Number of patients who completed the trial and had a full profile of olanzapine pharmacokinetics.

n.a. not available (could not be estimated).

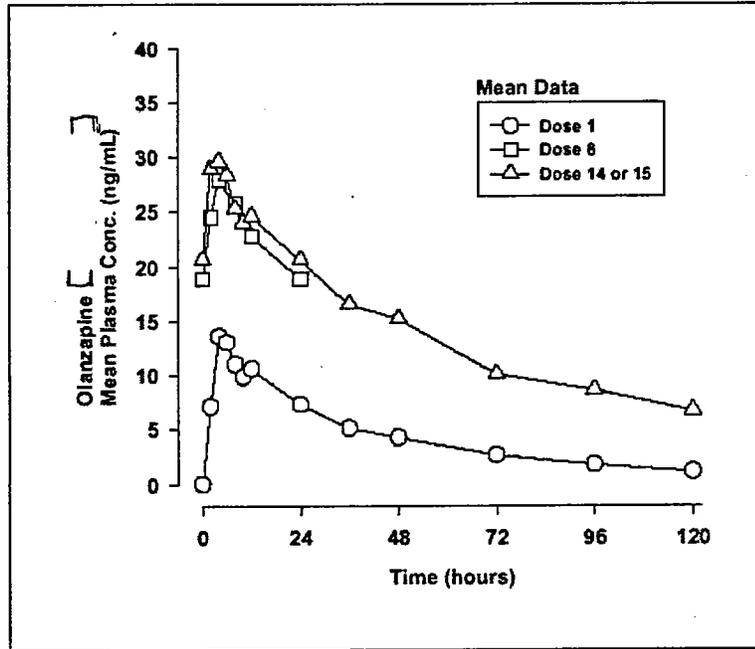
Observations:

- Upon multiple dose administration, concentrations of olanzapine and its metabolites had accumulated approximately two or three-fold higher than the single dose concentrations.

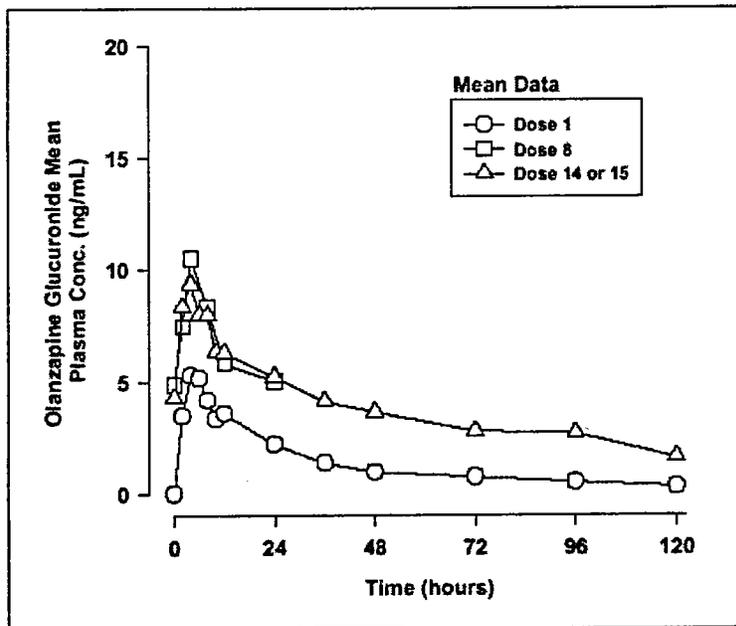
Mean Olanzapine plasma concentration profile after single and multiple doses is shown in the following figure:



Mean Olanzapine plasma concentration profile after single and multiple doses is shown in the following figure:



Mean Olanzapine glucuronide plasma concentration profile after single and multiple doses is shown in the following figure:



This study did not permit a rigorous and controlled evaluation of the impact of valproate on the pharmacokinetics of olanzapine, a comparison to historical pharmacokinetic characteristics for olanzapine and its metabolites was done by the sponsor.

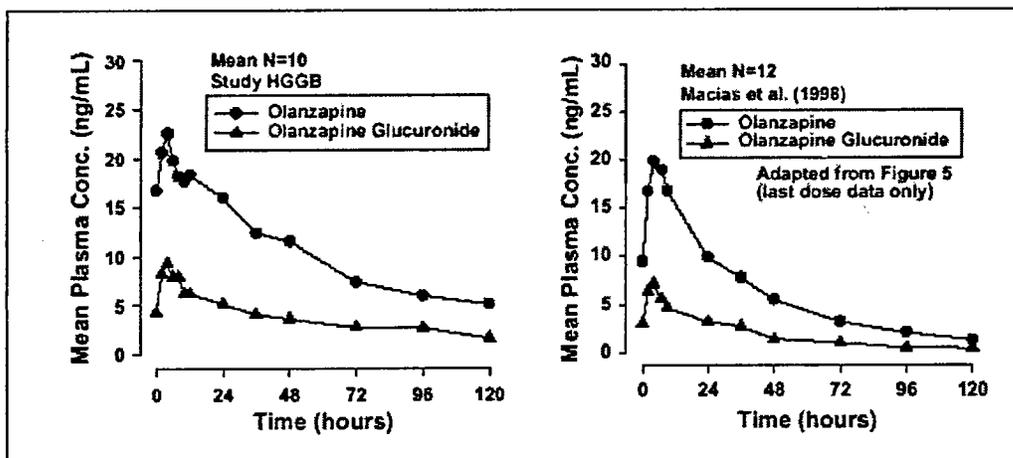
A steady state study (10 mg daily) conducted by Macias et. al. showed olanzapine and its glucuronide pharmacokinetic parameters to be similar to that obtained from this study. Comparative results are shown in the following Table:

Table: Mean (\pm SD) Olanzapine and its Glucuronide Pharmacokinetic Characteristics

Pharmacokinetic Characteristic	Macias et. al (1998) N=12	Study HGGB N = 10
OLANZAPINE		
C_{max} (ng/mL)	20.5 \pm 4.9	25.3 \pm 8.5
t_{max} (hrs)	5.5 \pm 1.6	3.9 \pm 3.2
AUC ₀₋₂₄ (ng \times hr/mL)	368 \pm 95.8	442 \pm 129
Half-Life (hrs)	36.0 \pm 5.1	38.7 \pm 11.6
CLp/F (L/hr)	29.4 \pm 9.4	24.9 \pm 9.2
$V\lambda z^F$ (L/kg)	19.2 \pm 6.2	13.2 \pm 2.9
OLANZAPINE GLUCURONIDE		
C_{max} (ng/mL)	8.2 \pm 3.1	10.6 \pm 6.1
t_{max} (hrs)	5.1 \pm 2.7	5.7 \pm 3.6
AUC ₀₋₂₄ (ng \times hr/mL)	118 \pm 55.7	153 \pm 112
Half-Life (hrs)	39.6 \pm 10.4	52.0 \pm 23.0

This comparison showed a 20-30% increase in C_{max} and AUC between studies. CL of olanzapine was 15% lower. Significance of these differences is unknown due to cross study comparisons.

Comparative profiles from the two studies is shown in the following figures:



From studies done by Callaghan et.al. (1999), the mean half-life was 33 hours ranging from 21 to 54 hours, mean apparent clearance was 26 L/hr ranging from 12 L/hr to 47 L/hr (also in the approved package insert).

These pharmacokinetic characteristics for olanzapine are consistent with the pharmacokinetic values observed for olanzapine in this study. Olanzapine half-life ranged from 24.9-63.5 hours (mean (38.7 hours) and CL ranged from 14.9 to 42.7 L/hr (mean 24.9 L/hr) in this study.

Valproic Acid:

Valproic acid concentrations were measured for therapeutic drug monitoring. The concentration was measured 12 hours before and after dosing. The data did not suggest any impact of olanzapine on the valproic acid concentrations. Statistical comparison of the local-laboratory valproic acid concentrations between the placebo and olanzapine groups confirmed that the two treatment regimens maintained similar therapeutic concentrations. The therapeutic concentration range for valproic acid extends from 50 µg/mL to 125 µg/mL.

- ◆ At the local laboratory, the placebo group registered a least-square mean concentration of 74.6 µg/mL while the olanzapine group yielded a least-square mean concentration of 71.1 µg/mL. These differences were not statistically different ($p=0.663$).
- ◆ At the central laboratory, the placebo group registered a least-square mean concentration of 73.0 µg/mL while the olanzapine group yielded a least-square mean concentration of 70.4 µg/mL. These differences were not statistically different ($p>0.5$).

Although the protocol permitted dose adjustments of divalproex to maintain therapeutic concentrations, the divalproex dosage was not changed except in one individual where the dosage was increased. Thus, an interpretation of the mean valproic acid concentrations reflects the impact of olanzapine on the exposure to fixed doses (although the divalproex dosage was variable between individual patients ranging from 500 to 2250 mg/day).

The impact of various doses of divalproex upon the observed plasma concentrations was also assessed. Individual patients were given divalproex doses of 500 mg to 2250 mg per day to maintain concentrations of valproic acid in the therapeutic concentration range (50 to 125 µg/mL).

The following figures show the relationship between the valproic acid dose and the achieved valproic acid plasma concentrations. The regression relationships are similar (not significantly different) between the placebo and olanzapine patient groups.

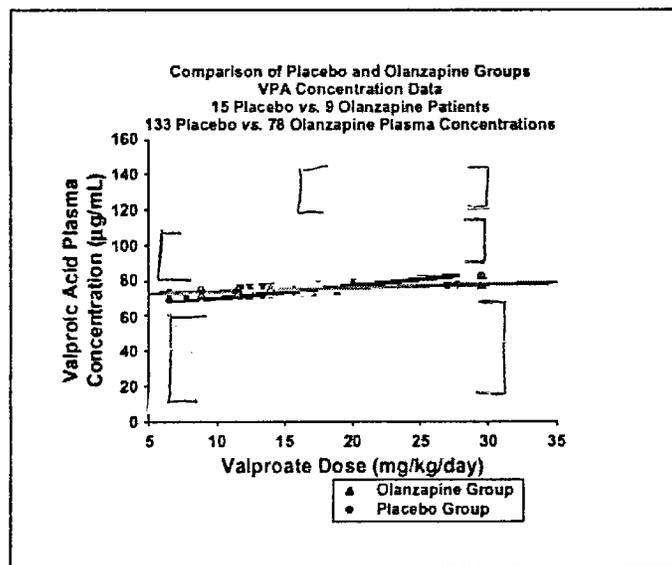
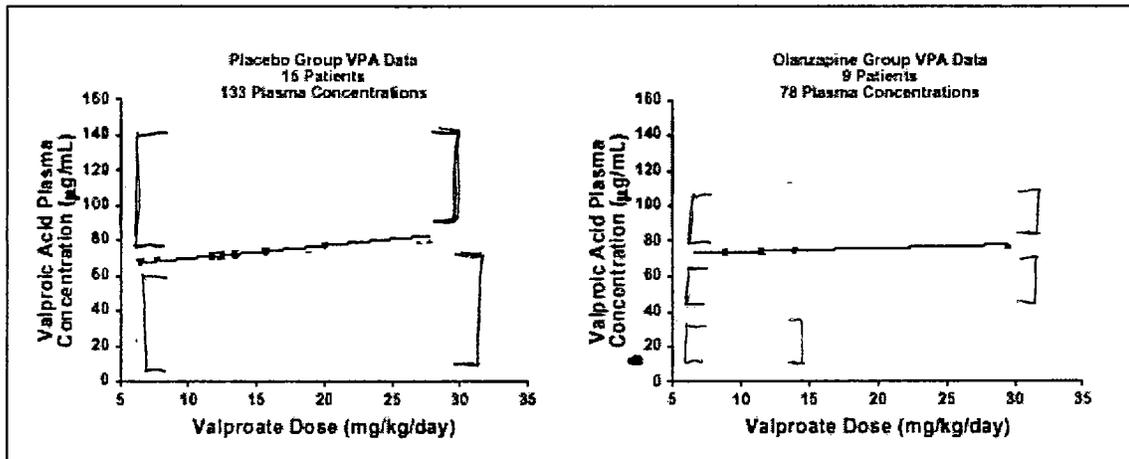


Table: Statistical Evaluation of the Regression between Valproic Acid Plasma Concentrations and Valproate Dose

Statistical Regression Line Testing	p-Value	Placebo Estimate	Olanzapine Estimate
Regression on Dose	0.055		
Inter-Treatment Comparison of Regression Intercepts	0.812	53.7	57.8
Inter-Treatment Comparison of Regression Slopes	0.642	0.017	0.010

The statistical analysis did not reveal any statistically significant differences in the plasma concentrations of valproic acid between the placebo group and the olanzapine group, or between the pretreatment versus co-administration within each treatment group.

Table: Statistical Evaluation of the Valproic Acid Plasma Concentrations between Treatment Groups and Within Each Treatment Group Pre-treatment and Combined Treatment^a

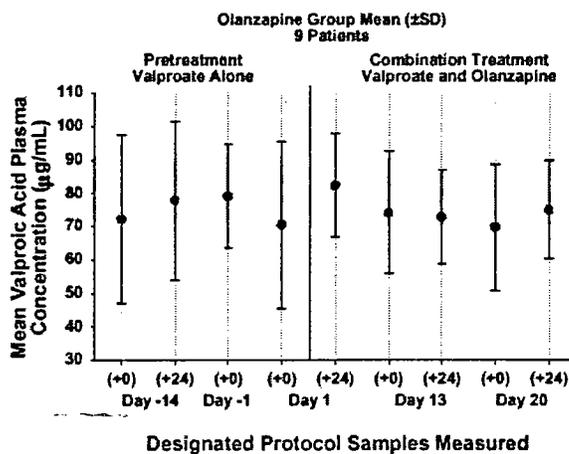
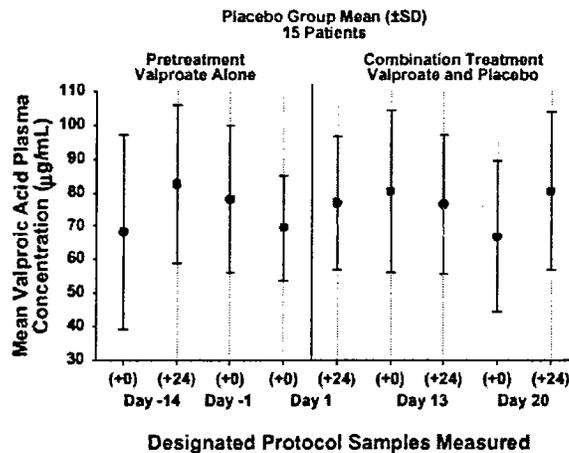
Treatment	Phase	LS Mean	Difference	p-Value ^b
Placebo	Pretreatment	73.0	2.2	0.592
	Co-administered	75.3		
Olanzapine	Pretreatment	70.4	0.6	0.911
	Co-administered	70.9		
Olanzapine difference minus Placebo difference ^c			-1.7	0.800

^a Values reported are rounded from the values given in the statistical printouts

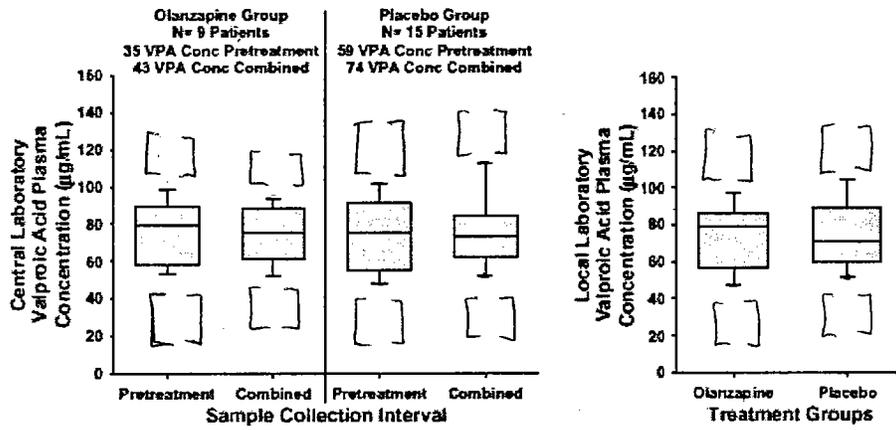
^b Adjusted for multiple comparisons

^c Olanzapine (Co-administered - Pre-Treatment) minus Placebo (Co-administered - Pre-Treatment)

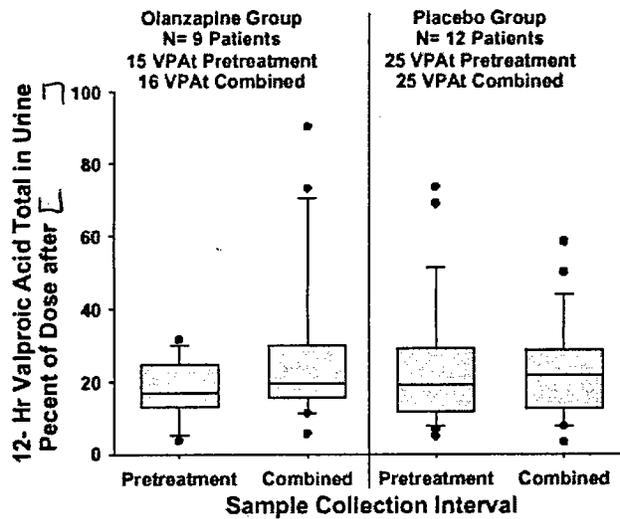
Further comparisons are shown in the following figures:



The following box plots show the central and local laboratories valproic acid plasma concentrations in the olanzapine and placebo groups.



The box plot showing the percentage of the dose excreted in the urine after [] of the urine sample is shown in the following figure.



Valproic acid metabolite concentrations were not measured.

Conclusions based on Pharmacokinetics:

It is difficult to assess the effect of valproate on olanzapine pharmacokinetics based on this study. Patients on stable doses of divalproex were enrolled in this study, therefore without the olanzapine control arm the study design did not permit a direct assessment of changes in olanzapine pharmacokinetics, such as would be possible in a classical crossover design. The sponsor has shown some historical comparisons of the data, which is not really a robust comparison. However, the pharmacokinetic data for olanzapine are similar to those in other studies and show a lack of any substantial difference from previous results. The package insert for olanzapine gives a wide range of half-life and clearance values and the data obtained from this study does fall within the range reported in the label.

The effect of olanzapine on valproate pharmacokinetics has been assessed by measuring valproic acid concentrations at 12 hours before and 12 hours after dosing. No significant difference in the plasma concentrations between the olanzapine and placebo group was observed.

Olanzapine is predominantly oxidized by cytochrome P450 (CYP) 1A2 and 2D6 (minor) while approximately 40% of a valproic acid dose undergoes mitochondrial beta-oxidation. CYP 2C9 and 2A6 oxidize about 15% of the valproic acid dose (*Sadeque AJM, Fisher MB, Korzekwa KR, Gonzalez FJ, Rettie AE. 1997; Human CYP2C9 and CYP2A6 mediate formation of the hepatotoxin α -4-ene-valproic acid. J Pharmacol Exp Ther 283(2):698-703*). In addition, both drugs are glucuronidated (40-50%), olanzapine undergoes N-glucuronidation. Valproic acid undergoes conjugation via UGT1A6, 1A8, and possibly 2B7 to form an ester glucuronide (*Levy RH, Mather GG, Anderson GD. 2000. Anticonvulsants. In Levy RH, Thummel KE, Trager WF, Hansten PD, and Eichelbaum M, editors. Metabolic Drug Interactions. Philadelphia: Lippincott Williams and Wilkins. p. 557-562*).

Any interaction based on CYP 450 metabolism is not likely because of the different pathways of metabolism. However, both drugs undergo glucuronidation. Hence, inhibition of the glucuronidation is possible to some extent. The study design was not robust to pick any small change that could occur due to possible inhibition of glucuronidation. The data from this study did not give any evidence towards a major pharmacokinetic drug interaction, any changes if possible are likely to be only small.

Two controlled clinical studies have also been performed to assess efficacy and safety of olanzapine in combination with divalproex and lithium in the treatment of bipolar mania.

Conclusions from Pharmacodynamic Evaluation:

The sponsor's conclusion regarding pharmacodynamic evaluation from this study is summarized here:

Statistical evaluation of CGI scores for mania, depression, and bipolar disorder disclosed no significant differences between the olanzapine + valproate and placebo + valproate groups. Because most enrolled patients were scored as not ill, it would be difficult to assess statistical improvement with these groups of patients. However, it is possible to

say that clinical deterioration was not observed for either group during the course of the study.

Alertness was evaluated by questionnaire. Statistical analyses for each question revealed a significant treatment difference for selected questions. In general, a decrease in alertness was noted. The differences occurred subsequent to the 10-mg single-dose administration of olanzapine, as observed in earlier studies in healthy subjects. These earlier studies tended to show adaptation of the responses with continued dosing. In this study as well, this observation was confirmed.

Two clinical studies have been conducted to evaluate efficacy and safety in combination with divalproex and lithium. The analyses of pivotal clinical studies as summarized by the sponsor suggested that olanzapine in a dose of 5, 10, 15, or 20 mg/day is an effective agent for the treatment of acute manic or mixed bipolar episodes, with or without psychotic features, when combined with lithium or valproate. For the combined primary efficacy analysis, the Y-MRS (Young-Mania Rating Scale) total score improvement in the olanzapine added to current mood stabilizer therapy group (-13.11) was statistically significantly greater than in the placebo added to current mood stabilizer therapy group (-9.10) ($p=.003$).

Conclusions from Safety Evaluation:

Ten patients experienced events after olanzapine treatment. The adverse events on olanzapine were generally those observed in prior studies and included asthenia, somnolence, dry mouth, and headache. One patient experienced akathisia, dyskinesia, hypertonia, myalgia, nervousness, anxiety, diarrhea, rhinitis, and abnormal thinking. The symptom complex may have been related to use of olanzapine.

In prior clinical pharmacology studies in healthy subjects, olanzapine did not show increases in the corrected QT interval. In this study, comparisons between treatment groups for the QTc (Bazett correction) showed no statistically significant differences. However, 1 patient given olanzapine had a post-treatment QTc interval >450 msec; the corrected QT interval was prolonged >30 msec more than her averaged control value. Because this change was observed only after single-dose olanzapine and not multiple-dose olanzapine, the clinical relevance of this is unknown and may not be related to olanzapine treatment.

Prolactin values also were increased during the olanzapine-divalproex treatment in comparison to the placebo-divalproex treatment.

No laboratory values (hematology, liver enzymes) were significantly different between the olanzapine and placebo groups that could be related to any clinical significance.

OVERALL CONCLUSIONS

The data for valproic acid plasma concentrations show that over the dosage range of

divalproex (500 to 2250 mg per day), the range of therapeutic concentrations for valproic acid (50-125 $\mu\text{g/mL}$) were not influenced substantially by coadministration of olanzapine (10 mg daily for 2 weeks). These results, therefore, support the conclusion that olanzapine does not affect the pharmacokinetics of divalproex.

Since patients on stable doses of divalproex were enrolled in this study, the study design did not permit a direct assessment of changes in olanzapine pharmacokinetics, such as would be possible in a classical crossover design. Nevertheless, the pharmacokinetic data for olanzapine are similar to those in other studies and the lack of a substantial difference from previous results suggests that valproic acid does not substantially affect the pharmacokinetics of olanzapine.

APPEARS THIS WAY
ON ORIGINAL

ASSAY VALIDATION

Olanzapine in human plasma:

Method type: HPLC with
Limit of Quantitation: 0.25 ng/mL
Validation range: 0.250 ng/mL to 50.0 ng/mL,
0.250 ng/mL to 100 ng/mL (SAP 820-0192).
Validation accuracy: The inter-day range of accuracy during validation was 5.1% to 11.7% RE for olanzapine.

Validation precision: The inter-day range of precision during validation was 1.7% to 2.4% RSD for olanzapine.

Stability: Matrix: 48 hours at room temperature for olanzapine
Extract: 48 hours at room temperature for olanzapine
F/T: 5 cycles at approximately -80°C for olanzapine
Long term in matrix: 7 months at approximately -80°C for olanzapine and metabolites; 16 months at approximately -20°C for olanzapine; at least 10 months for olanzapine at approximately -60°C.

Valproic Acid in Human Plasma:

Method type: GC with
Limit of Quantitation: 10 µg/mL
Validation range: 10.0 µg/mL to 250 µg/mL.
Validation accuracy: 1.5% to 2.8%
Validation precision: 1.6% to 5.9%
Stability: Valproic Acid is stable in Human Plasma for 24 hours at ambient temperature. Processed Human Plasma samples are stable for 48 hours at ambient temperature.

Valproic Acid in Human Urine:

Method type: GC with
Limit of Quantitation: 40 µg/mL
Validation range: The validated calibration curve range is 40.0 to 1000 µg/mL. Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range.
Validation accuracy: -0.4% to 0.4%
Validation precision: 1.5% to 1.8%
Stability: Valproic Acid in Human Urine is stable for 24 hours at ambient temperature. The processed samples are stable for 4 days at ambient temperature.

FILING AND REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics			
<i>New Drug Application Filing and Review Form</i>			
General Information About the Submission			
	Information		Information
NDA Number	N20-592 (SE1-018)		Brand Name ZYPREXA
OCPB Division (I, II, III)	I		Generic Name Olanzapine
Medical Division	120		Drug Class selective monoaminergic antagonist
OCPB Reviewer	Veneeta Tandon		Indication(s) The combination of ZYPREXA with lithium or valproate is indicated for the treatment of acute manic episodes.
OCPB Team Leader	Ramana Uppoor		Dosage Form Fast Disintegrating Tablets
			Dosing Regimen Begin with 10 mg QD. No information on doses greater than 20 mg QD. To be dosed with a particular dose range of lithium or valproate
Date of Submission	9/16/02		Route of Administration Oral
Estimated Due Date of OCPB Review	4/25/02		Sponsor Eli Lilly and Co.
PDUFA Due Date	7/16/02		Priority Classification 6S
Division Due Date	5/1/02		
Background: Olanzapine has been approved for the treatment of schizophrenia and bipolar mania as monotherapy. This efficacy supplement is for the treatment of bipolar mania as a combination therapy with mood stabilizers, lithium and valproate. An efficacy study has also been conducted in combination with the mood stabilizers for the treatment of bipolar I disorders. Clinical study evaluated doses in the range of 5-20 mg per day for 6 weeks.			
Clin. Pharm. and Biopharm. Information			
	"X" if included at filing	Number of studies submitted	Number of studies reviewed
STUDY TYPE			
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary			
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		Validation provided
I. Clinical Pharmacology			
Mass balance:			
Isozyme characterization:			
Blood/plasma ratio:			
Plasma protein binding:			
Pharmacokinetics (e.g., Phase I) -			
Healthy Volunteers-			
single dose:			
multiple dose:			
Patients-			
single dose:			
multiple dose:			
Dose proportionality -			
fasting / non-fasting single dose:			
fasting / non-fasting multiple dose:			
Drug-drug interaction studies -			
In-vivo effects on primary drug:			

In-vivo effects of primary drug:	X	1		Drug interaction study with valproate (divalproex sodium) Cross reference to NDA 20-592 for drug interaction study with lithium (Study E001)
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
AIDS patients				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		1		
Total Number of Studies			1	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		None		
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> Is there a drug interaction between olanzapine and valproic acid? Are appropriate doses evaluated in this drug-drug interaction study? 		

Other comments or information not included above	PK datasets have not been submitted, but will be submitted within 45 days of the submission date. Safety datasets from this study have been provided electronically.
Primary reviewer Signature and Date	Veneeta Tandon, Ph.D
Secondary reviewer Signature and Date	Ramana Uppoor, Ph.D

CC: NDA 20-592, HFD-850(Electronic Entry or Lee), HFD-120(CSO), HFD-860(Uppoor, Sahajwalla,
Meh

APPROVED BY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Veneeta Tandon .
3/17/03 11:14:29 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
3/17/03 11:34:24 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-592/S-018

ADMINISTRATIVE and CORRESPONDENCE

ITEM 13: PATENT INFORMATION

NDA 20-592 Zyprexa (olanzapine)

The undersigned declares that the following patent covers the formulation, composition, and/or method of use of olanzapine as indicated. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act and is the subject of this supplemental application for which approval is being sought:

Patent Number	Patent Expiry Date	Type of Patent (Drug Substance, Drug Product, or Method of Use)	Patent Owner's Name
U.S. 5,229,382	April 23,2011	Compound, formulation, method of use	Eli Lilly and Company

The above patent is all owned or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana.



Name of authorized official
Director, US Regulatory Affairs

9/5/02

Date

ITEM 14: PATENT CERTIFICATION

NDA 20-592 Zyprexa (olanzapine)

EXCLUSIVITY

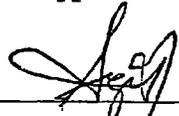
Eli Lilly and Company (Lilly) claims a three year period of exclusivity for the use of olanzapine in combination with lithium or valproate for the short-term treatment of acute manic episodes associated with Bipolar I Disorder as provided by 21 C.F.R. 314.108(b)(5).

Clinical trials conducted which are essential to approval of this supplemental NDA are identified as follows:

F1D-MC-HGFU Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder

As required by 21 C.F.R. 314.50(j)(4), Lilly certifies that to the best of Lilly's knowledge:

1. the above clinical investigation included in this supplemental application meets the definition of "new clinical investigation" as set forth in 21 C.F.R. 314.108(a);
2. the above clinical investigation is "essential to approval" of this supplemental application. Lilly, through its employees and others, electronically searched the Scientific literature (as of 31 March 2002) via Medline, Derwent Drug File, SciSearch, Embase, PsychINFO, Biosis, and World Patent Index and has not discovered any published studies or publicly available reports for which Lilly is seeking approval. In Lilly's opinion and to the best of Lilly's knowledge, there are no published studies or publicly available reports to provide a sufficient basis for the approval of the conditions for which Lilly is seeking approval without reference to the new clinical investigations in this application.
3. the above clinical investigations were each conducted or sponsored by Lilly. Lilly was the sponsor named in the Form FDA-1571 of IND number 28,705 under which the new clinical investigation(s) that is essential to the approval of this application was conducted.



Name of authorized official
Director, US Regulatory Affairs

9/1/02

Date

EXCLUSIVITY SUMMARY for NDA # 20592 SUPPL # SE1-018

Trade Name ZYPREXA Generic Name OLANZAPINE

Applicant Name ELI LILLY & CO. HFD- 120

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/___/ NO /___/

b) Is it an effectiveness supplement? YES // NO /___/

If yes, what type(SE1, SE2, etc.)? SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES // NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

ADJUNCTIVE THERAPY W. LITHIUM OR VALPROATE
IN THE TX OF ACUTE MANIC OR MIXED EPISODES
ASSOCIATED W. BIPOLAR I DISORDER

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

THREE

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-592 (ORIG. SUBMISSION)

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO //

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval: *ONLY ONE STUDY NEEDED*

Investigation #1, Study # PLD-MC-HGFU

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO //

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO //

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # FID-MC-HGFU

Investigation # __, Study # _____

Investigation # __, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 28, 70 YES / / NO / ___ / Explain: _____

Investigation #2
IND # _____ YES / ___ / NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES / ___ / Explain _____ NO / ___ / Explain _____

Investigation #2
YES / ___ / Explain _____ NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/

NO //

If yes, explain: _____

Dr. J. P. Bates Ph.D.
Signature of Preparer
Title: *Reg. Project Mgr.*

7-8-03
Date

[Signature]
Signature of Office or Division Director

8/14/03
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 20-592 Supplement Type (e.g. SE5): SE1 Supplement Number: 018

Stamp Date: SEP. 17 2002 Action Date: _____

HFD 120 Trade and generic names/dosage form: ZYPREXA (OLANZAPINE) TABLETS

Applicant: ELI LILLY & CO. Therapeutic Class: ANTIMANIC

Indication(s) previously approved: SCHIZOPHRENIA, MANIA (ACUTE)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: ADJUNCTIVE TX ACUTE MANIC/MIXED EPISODES BIPOLAR I

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: MONOTHERAPY FOR MANIA IS BEING STUDIED IN PEDI

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: *Dr. [Signature]*
{See appended electronic signature page} 7-8-03

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

As a Phase 4 commitment for the bipolar mania monotherapy indication, Lilly is conducting a 3-week placebo-controlled study of olanzapine monotherapy in adolescent patients (ages 13 to 17 years) diagnosed with manic or mixed episode associated with bipolar I disorder (with or without psychotic features). However, Lilly does not intend to conduct studies in the pediatric population (ages birth to 17 years) to evaluate olanzapine in combination with lithium or valproate for the treatment of manic or mixed episodes associated with bipolar I disorder since a pediatric waiver was granted during the May 30, 2002 pre-NDA meeting (see FDA meeting minutes issued July 2, 2002).

APPLICABLE THIS WAY
ON ORIGINAL

Debarment Certification

NDA Application No.: 20-592

Drug Name: Zyprexa® (olanzapine)

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: 

Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs

9/5/02
September 5, 2002

Format of Financial Disclosure Information

The Financial Disclosure information is provided for Protocol F1D-MC-HGFU in a table format listing the investigators (including sub-investigators) and status of disclosure. We have also defined the due diligence process used to obtain the information. Since this covered study did not require disclosure, FDA Form 3454 is presented prior to the table, certifying that each investigator had nothing to disclose or for whom disclosure was not obtained. In cases where disclosure information was not obtained, the reason for this is provided.

Due Diligence Process for Collection of Financial Disclosure Information

The current Lilly procedure for obtaining financial disclosure information is to send a cover letter and form to each investigator (including principal investigator, co-investigator, and sub-investigator) prior to the beginning of each site's participation in the study. Because Protocol HGFU was initiated prior to the effective date for the Financial Disclosure final rule and the first release of the Lilly global policy statement on collection of financial disclosure, the cover letters and forms were mailed to each investigator at the completion of the study. For those sites where financial disclosure information was not received, an additional letter and form were sent to each investigator. If this attempt at obtaining the financial disclosure information failed, a certified letter was sent and follow-up telephone calls were made to the sites. If the information could not be obtained following numerous requests, specific documentation was noted and filed appropriately in the study files.

APPEARS THIS WAY
ON ORIGINAL

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mauricio Tohen, M.D., Dr. P.H.	Medical Director
FIRM/ORGANIZATION	
Eli Lilly and Company	
SIGNATURE	DATE
	Sept 6, 2002

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Redacted 10 page(s)

of trade secret and/or

confidential commercial

information from

Clinical Investigator / Financial Disclosure

Minutes of Meeting
NDA 20-592 / SE1-018: Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, 20 mg
Eli Lilly & Co.: Bipolar Disorder, Adjunctive with Lithium or Valproate
Supplemental NDA Filing Meeting

DATE: October 30, 2002 (9:00 – 10:00 a.m.) **LOCATION:** WOC II Rm. 4034
PARTICIPANTS: R. Katz, T. Laughren, E. Hearst, O. Siddiqui, L. Stockbridge, R. Uppoor, V. Tandon, N. Khin, D. Bates
ADDITIONAL CONTRIBUTORS: T. Oliver, K. Jin, S. McLamore

Background: Olanzapine is currently approved in the treatment of acute manic episodes (S-006). The original and only other current approved indication is schizophrenia. S-018 is a standard efficacy supplement proposing the use of olanzapine as adjunctive therapy in the treatment of acute manic episodes, in combination with lithium or valproate.

Summary: The supplemental NDA is an all-electronic submission and was found fileable in all pertinent disciplines. It is classified 6S (approved chemical entity, new indication, standard priority). The action due date is July 17, 2003. This action will require Dr. Katz' signature. All reviews should be completed by May 1, 2003.

Discussion: *CMC:* Drs. Oliver and McLamore have informed the RPM that the submission is fileable for CMC; only the request for categorical exclusion (EA) requires CMC review.
Pharm/Tox: No P/T review is needed; no new pharm/tox data and no pharm/tox related additions or revisions to labeling are included in the supplement.
Clin Pharm/Biopharmaceutics: The pharmacokinetic datasets were not included in the original submission but were submitted ten days later (September 26, 2002). All datasets have now been posted to the EDR. The submission is fileable for Biopharmaceutics review.
Clinical: The submission is fileable for clinical review, with no significant issues identified.
DSI: A DSI audit will be performed for two US sites (Dr. Logue, Homewood, AL, and Dr. Weisler, Raleigh-Durham, NC).
Statistics: The submission is fileable for statistics.
DDMAC: No filing issues were identified by DDMAC.
Regulatory / Project Management (with Post Meeting Notes): All team members have EDR access. User Fees were paid prior to supplement submission. The firm has previously requested a waiver of the requirement for pediatric studies, which was granted (May 30, 2002). The acknowledgement/filing letter for the supplement will address these points. Since no specific filing questions were raised at this time, the letter will not include any detailed questions.

There were no objections to filing the supplemental NDA. It was officially filed as of this date. The Lilly contact person, Ms. Michele Sharp, was telephoned and informed of the filing decision immediately following the meeting (voice mail).

Post Meeting Note: The filing letter was transmitted to the firm on November 4, 2002 (e-mail).

Please see electronic signature page

Doris J. Bates, Ph.D.
Regulatory Project Manager
For the attendees

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Doris Bates

6/23/03 02:47:33 PM

Signed by Dr. Bates with prior concurrence by Dr. Laughren

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: February 24, 2003

TO: Doris Bates, Ph.D., Regulatory Project Manager
Earl Hearst, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 20-592/SE1-018

APPLICANT: Lilly

DRUG: Zyprexa (olanzapine)

THERAPEUTIC CLASSIFICATION: Type S

INDICATION: Add-On Therapy in Bipolar Disorder, Mania

CONSULTATION REQUEST DATE: October 30, 2002

ACTION GOAL DATE: July 17, 2003

I. BACKGROUND:

Olanzapine (Zyprexa) is an atypical antipsychotic agent and it is approved for use in treatment of schizophrenia. In the supplement NDA application, the sponsor has requested the use of olanzapine added to mood stabilizers in treatment of bipolar disorder. The application is based on protocol F1D-MC-HGFU designed as 2 randomized, double-blind, parallel studies. Subjects with a DSM-IV diagnosis of bipolar I disorder and display an acute manic or mixed episode (with or without psychotic features) were included in the study. The primary study objective was to compare the efficacy and safety of olanzapine 5-20mg/day versus placebo added to mood

stabilizer (lithium or valproate).

Inspection assignment was issued on November 13, 2002 for 2 U.S. sites: Drs. Logue and Weisler. These investigators were the high enrollers for the protocol.

II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Dr. Logue	Homewood	AL	11-13-2002	01-16-2003	NAI
Dr. Weisler	Raleigh	NC	11-13-2002	01-23-2003	VAI

LOGUE, M.D.

At this clinical site, 49 subjects were screened; 30 subjects were randomized to receive either olanzapine (5-20mg/day) or Placebo added to mood stabilizers (lithium or valproate) for treatment of Bipolar Disorder.

An audit of 49 subjects' records was conducted. No FDA Form-483 was issued. No major objectionable conditions noted. Data appear acceptable.

WEISLER, M.D.

At this clinical site, 45 subjects were screened; 39 subjects were randomized. A total of 30 subjects completed the study. Nine subjects were discontinued. Reasons for discontinuation included lost to follow up (4 subjects), patient's decision (3 subjects), lack of efficacy (1 subject), and adverse event (1).

An audit of 10 subjects' records was conducted. Inspection findings included that for subject 1505, changes were made on the current major depressive or manic episode checklist to indicate that the subject met the responder criteria at visit 8. For subject 1514, it was noted to have inconsistent visit 2 dates in performing Young Mania Rating Scale (YMRS). We also note that subject 1514's valproate dose was adjusted in the study period I. As specified in the protocol, subject who needed the dose of mood stabilizer adjusted during this study period should have been discontinued from the study. All subjects signed the informed consent. Overall, data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Although some deficiencies were noted at Dr. Weisler's site as stated above, data from these sites appear acceptable for use in support of this NDA supplement.

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviations(s) from regulations. Data acceptable

VAIr= Deviation(s) form regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable

Pending = Inspection not completed

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

cc:

NDA 20-592/SE1-018

Division File

HFD-45/Program Management Staff (electronic copy)

HFD-47/c/r/s

HFD-47/Khin

HFD-47/Friend

HFD-45/RF

rd: NK:02/24/03

O:\NK\CIS\NDA 20592SE1018 Zyprexa addon bipolar CIS.DOC

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ni Aye Khin

2/25/03 10:09:13 AM

MEDICAL OFFICER

Original DSI paper version of this summary was initialed
and concurred by Dr. A. El-Hage on 2/24/03

Richard H. Weisler, M.D.
900 Ridgefield Drive, Suite 320
Raleigh, North Carolina 27609

MAR - 3 2003

Dear Dr. Weisler:

Between December 18 and 30, 2002, Ms. Barbara M. Frazier, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol F1D-MC-HGFU entitled "Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder) of the investigational drug olanzapine (Zyprexa), performed for Lilly. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

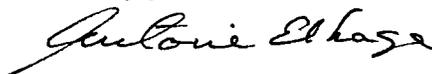
From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Frazier presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your letter dated January 8, 2003 and we wish to emphasize the followings:

- 1) For subject 1505, changes were made on the current major depressive/manic episode checklist to indicate that the subject met the responder criteria at visit 8 [21 CFR 312.62(b)]
- 2) For subject 1514, you adjusted the dosage of mood stabilizer based on the blood level prior to visit 2. As specified in the protocol, subject who needed the dose of mood stabilizer adjusted during this study period should have been discontinued from the study [21 CFR 312.60].

We acknowledge your assurances that corrective actions will be taken to prevent similar findings from occurring in any future studies.

We appreciate the cooperation shown Investigator Frazier during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,



Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 2 – Richard H. Weisler, M.D.

FEI: 3003844032

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

X inadequate and inaccurate records (06)

X failure to adhere to protocol (05)

cc:

HFA-224

HFD-120 Doc.Rm. NDA 20-592/SE1-018

HFD-120 Review Div.Dir. Katz

HFD-120 MO Hearst

HFD-120 PM Bates

HFD-47 c/r/s GCP File #10796

HFD-47 MO Khin

HFD-47 CSO Friend

HFR-SE150 ATL-DO DIB Todd-Murrell

HFR-SE150 Bimo Monitor Hubbard

HFR-SE1535 Field Investigator Frazier

GCF-1 Seth Ray

r/d:NK:2/20-2/21/03; 2/24/03

reviewed:AEH:2/21/03

f/t:ml:2/24/03

O:\NK\Letters\Weisler.vai.doc

Reviewer Note to Rev. Div. M.O.

- At this clinical site, 45 subjects were screened; 39 subjects were randomized to receive either olanzapine (5-20mg/day) or Placebo added to mood stabilizers (lithium or valproate) for treatment of Bipolar Disorder.
- An audit of 10 subjects' records was conducted.
- Inspection findings included: 1) changes were made on the current major depressive/manic episode checklist for subject 1505 to indicate that the subject met the responder criteria at visit 8; and 2) for subject 1514, it was noted to have inconsistent visit 2 dates in performing YMRS.
- We also note that subject 1514's valproate dose was adjusted in the study period I.
- Overall, data appear acceptable.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Bader
Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 24 2003

Edward H. Logue, M.D.
One Independent Plaza, Suite 900
Homewood, Alabama 35209

Dear Dr. Logue:

On January 7 and 8, 2003, Ms. Patricia S. Smith, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol F1D-MC-HGFU entitled: "Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder) of the investigational drug olanzapine, performed for Eli Lilly and Company. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Smith during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 2 – Edward H. Logue, M.D.

FEI: 3000205386

Field Classification: Refer to HFD-47

Headquarters Classification:

- 1)NAI
 2)VAI- no response required
 3)VAI- response requested
 4)OAI

cc:

HFA-224
HFD-120 Doc.Rm. NDA 20-592/SE1-018
HFD-120 Review Div.Dir. Katz
HFD-120 MO Hearst
HFD-120 PM Bates
HFD-47 c/r/s GCP File #9081
HFD-47 MO Khin
HFD-47 CSO Friend
HFR-SE340 NOL-DO/NSV-BR DIB Lewis
HFR-SE350 Bimo Monitor Abel
HFR-SE3555 Field Investigator Smith
GCF-1 Seth Ray

r/d:NK:1/21/03

reviewed:AEH:1/22/03

f/t:ml:1/22/03

O:\NK_Letters\Logue 012003.nai.doc

Reviewer Note to Rev. Div. M.O.

- At this clinical site, 49 subjects were screened; 30 subjects were randomized to receive either olanzapine (5-20mg/day) or Placebo added to mood stabilizers (lithium or valporate) for treatment of Bipolar Disorder.
- An audit of 49 subjects' records was conducted.
- No FDA Form-483 was issued.
- Data appear acceptable.



www.lilly.com

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

November 13, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

**Re: NDA 20-592 (S018), Zyprexa® (olanzapine)
Use of Zyprexa in combination with lithium or valproate for the treatment of acute
manic episodes associated with bipolar disorder**

We are amending the subject referenced supplemental NDA (submitted on September 16, 2002) with a request for categorical exclusion from the environmental assessment requirement.

Pursuant to 21 CFR 25.15(d) and under 21 CFR 25.31(a), we claim the categorical exclusion from the requirement for an environmental assessment to support the proposed labeling change regarding the use of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder. To the best of our knowledge, no extraordinary circumstances exist.

Please call me at (317) 277-8382 if you require any additional information or if there are any questions. Alternatively, you may contact Dr. Gregory T. Brophy, Ph.D., Director, U.S. Regulatory Affairs at (317) 277-3799. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



Michele Sharp, PharmD
Regulatory Research Scientist
U.S. Regulatory Affairs

cc: Doris Bates, Ph.D.

Answers That Matter.



PRIOR APPROVAL SUPPLEMENT
ACKNOWLEDGED AND FILED:
NO FILING ISSUES IDENTIFIED

NDA 20-592/S-018

Eli Lilly and Company, Inc.
Attention: Greg Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your supplemental new drug application, submitted and received under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the use of ZYPREXA as adjunctive therapy to lithium or valproate in the treatment of bipolar disorder.

Date of Supplement: September 16, 2002
Date of Receipt: September 17, 2002
Supplement Number: S-018.

We also note your submission of September 26, 2002, to this supplement.

Your payment of the User Fee was effective September 17, 2002 (ID # 4411). The official date for this application to be filed under section 505(b) of the Act is November 15, 2002, in accordance with 21 CFR 314.101(a). The ten-month user fee goal date will be July 17, 2003.

We have completed our filing review of your application, and it has been filed, effective October 30, 2002, as confirmed in a voicemail message left with Ms. Michele Sharp of your firm on that date. At this time, we have not identified any potential review issues. However, the filing review is only a preliminary review; deficiencies may be identified during our substantive review of your application.

We also note your request for a waiver of the requirement for pediatric studies, to which we agreed (as you also note) at our pre-sNDA meeting of May 30, 2002. As you may be aware, the Pediatric Rule has recently been challenged in court. Therefore, the conditions applicable to pediatric studies in general will ultimately depend upon the resolution of that situation. *Ad interim*, the granting of your waiver request still stands, and we would not anticipate reversing this specific decision if the Rule is ultimately upheld. Please note that Pediatric Exclusivity provisions are unaffected by the recent court action.

If you have any questions, please contact the undersigned at (301) 594-2850 or via e-mail at batesd@cderr.fda.gov.

Sincerely,

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug
Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Doris Bates

11/4/02 01:33:15 PM

This letter includes filing language per PDUFA III because
it was filed after October 1. It is
not a filing letter per se because the
supplement was received prior to October 1.

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, October 30, 2002 10:28 AM
To: Tandon, Veneeta
Subject: FW: NDA 20-592 / SE1-018: New Efficacy Supplement: Amendment with PK Datasets and Cat. Exclusion

Hi - I actually did send the EDR address for the PK dataset, but it is inside the email attached to this message. You will need to open the e-mail in order to get the EDR hotlink.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research
FDA

-----Original Message-----

From: Bates, Doris J
Sent: Tuesday, October 01, 2002 2:43 PM
To: Katz, Russell G; Laughren, Thomas P; Jin, Kun; Baweja, Raman K; Uppoor, Ramana S; Stockbridge, Lisa L; Khin, Ni Aye; Hearst, Earl D; Siddiqui, Ohidul I
Cc: Tandon, Veneeta; Oliver, Thomas F
Subject: NDA 20-592 / SE1-018: New Efficacy Supplement: Amendment with PK Datasets and Cat. Exclusion

Hi everybody - the EDR has posted Lilly's amendment with the PK datasets. It also includes a claim for categorical exclusion (EA). Tom (Oliver), the CE is in the cover letter.

Here's the e-mail (again sent to me courtesy of Steve Hardeman, bless him).



FW: EDR - NDA
020592 from LILL...

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research
FDA

Bates, Doris J

Subject: NDA 20-592 / SE1-018: New Efficacy Supplement Filing Meeting: Zyprexa with Lithium or Valproate in Tx of Acute Manic Episodes in Bipolar Disorder
Location: CDER WOC2 4FL-E Conf Room
Start: Wed 10/30/02 9:00 AM
End: Wed 10/30/02 10:00 AM
Recurrence: (none)
Meeting Status: Meeting organizer
Required Attendees: Bates, Doris J; Katz, Russell G; Laughren, Thomas P; Jin, Kun; Baweja, Raman K; Uppoor, Ramana S; Stockbridge, Lisa L; Khin, Ni Aye; Hearst, Earl D; Siddiqui, Ohidul I
Optional Attendees: Tandon, Veneeta
Resources: CDER WOC2 4FL-E Conf Room

EDR address below:

http://edr/loadfile.asp?PATH=FILE://\CDSesub1\N20592\S_018\2002-09-16&DOCUMENT_ID=2358639&APPL_NO=020592&APPL_TYPE=N

WORD file of company's proposed labeling attached:



.YProposed_Word.do

C

Supplement dated 9/17/02, received 9/18/02, UF paid, filing date 11/15/02, action due date (10 mos) 7/17/03.

Note: PK datasets for clin pharm study (F1D-MC-HGGB) which should be included in the submission under Item 6. are not yet in submission. Applicant indicates that datasets will be submitted within 45 days or less of submission date. I have notified applicant that datasets are urgently needed and should be provided before filing meeting. Received

Please inform me of reviewer assignments ASAP so that I can add them to meeting. With e-submissions I do not always get the hard copy assignment forms right away (the EDR notice was sent to Steve Hardeman today, who forwarded it to me).

I will send consults to Biopharm, Stats ASAP. [DSI: the list of investigators and sites is in the EDR submission as Appendix 16.1.3., pp. 1261-1272, and I have printed out a copy. Please email if you would like hard copy.]

Bates, Doris J

From: Khin, Ni Aye
Sent: Wednesday, October 30, 2002 4:37 PM
To: Hearst, Earl D; Bates, Doris J
Cc: Friend, Brenda
Subject: NDA 20-592/SE1-018 Olanzapine Added to Mood stabilizers in Bipolar

Hi Earl and Doris,

As discussed, DSI will inspect the following sites for protocol F1D-MC-HGFU (acute therapy):

Center 018 Logue (N=49)
Center 030 Weisler (N=45)

E
Thanks.

J

--Ni

**Appears This Way
On Original**

Phone 317 276 2000

September 26, 2002

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

**Re: NDA 20-592, Zyprexa® (olanzapine) – Efficacy Supplement
Use of Zyprexa in combination with lithium or valproate for the treatment of acute manic
episodes associated with bipolar disorder**

We are amending the subject supplemental NDA (submitted on September 16, 2002) with the submission of pharmacokinetic datasets from Study F1D-MC-HGGB and a request for categorical exclusion from the environmental assessment requirement.

These datasets are provided in electronic format on CD Rom. The submission size is less than 1 megabyte. All electronic media have been checked by representatives of Lilly Information Technology and have been verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 40918h created on September 18, 2002 or later and Scan Engine 4.1.0.6.

With respect to an environmental analysis, we claim the categorical exclusion from the requirement for an environmental assessment to support the proposed labeling change regarding the use of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder.

Please call me at (317) 277-8382 if you require any additional information or if there are any questions. Alternatively, you may contact Dr. Gregory T. Brophy, Ph.D., Director, U.S. Regulatory Affairs at (317) 277-3799. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Michele Sharp, PharmD
Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosure

cc: Doris Bates, Ph.D.

www.lilly.com

SE1-018
Rec'd 17 Sep 02
Due 17 Jul 03
WF Paid 17 Sep 02

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

September 16, 2002

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

**Re: NDA 20-592, Zyprexa® (olanzapine) – Efficacy Supplement
Use of Zyprexa in combination with lithium or valproate for the treatment of acute
manic episodes associated with bipolar disorder**

This letter accompanies Eli and Lilly and Company's supplemental New Drug Application (sNDA) for Zyprexa for the use of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder. Substantial evidence of effectiveness supporting this indication is provided in the enclosed application based on two randomized, double-blind placebo-controlled studies (Protocol HGFU).

The enclosed Note to Reviewers provides a summary of previous relevant communications between the Agency and Eli Lilly and Company, and other specific submission information regarding this sNDA.

This sNDA is submitted in electronic format according to the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs." As specified in this Guidance, a paper review copy containing 21 volumes is included in this submission. The complete sNDA is provided in electronic format on CD Rom. The submission size is approximately 650 megabytes. All electronic media have been checked by representatives of Lilly Information Technology and have been verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 40910d created on September 10, 2002 and Scan Engine 4.1.0.6.

The User Fee of \$156,660 for this submission has been paid under User Fee number 4411. Form 3397 has been provided.

A Debarment Certification has been provided.

Reference is made to the agreement between FDA and Lilly with respect to the reporting of financial information for investigators who participated in the pivotal efficacy trials. This agreement is summarized in the Summary of Previous Communications section of the Note to Reviewers of this sNDA. Form 3454 has been provided along with accompanying information as requested by FDA.

To coordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications, concerning this file, regardless of subject, be directed to:

Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

FAX number: (317) 433-2255

Any calls regarding this submission should be made to:

Michele L. Sharp, PharmD
(317) 277-8382 (work)

[]

or alternatively you may reach Dr. Sharp via E-mail at Sharp_Michele@lilly.com.

In the case of Dr. Sharp's absence, please contact:

Mauricio Tohen, M.D.
(317) 277-9585 (work)

[]

You may also contact:

Gregory T. Brophy, Ph.D.
(317) 277-3799 (work)

[]

Any calls relating to functionality of the electronic portion of the submission should be made to:

Patrick Q. Mooney
(317) 276-0586 (work)

[]

On holidays, Saturdays or Sundays, call Dr. Sharp or Dr. Brophy at home using the telephone numbers indicated.

Close liaison between the representatives of Lilly listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Sincerely,

ELI LILLY AND COMPANY



fa: Michele L. Sharp, PharmD
Regulatory Research Scientist
U.S. Regulatory Affairs

cc: Doris Bates, Ph.D.

NOTE TO REVIEWERS
NDA 20-592, Zyprexa (olanzapine) – Efficacy Supplement
Use of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder.

INTRODUCTION

The intent of Eli Lilly and Company is to gain approval for the use of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder.

Substantial evidence of effectiveness supporting this use is provided in the enclosed application based on two randomized, double-blind placebo-controlled studies (Protocol F1D-MC-HGFU: Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder) that have been conducted under IND 28,705 (submitted July 25, 1997).

Since a pediatric waiver was granted during the May 30, 2002 pre-NDA meeting, Lilly does not intend to conduct studies in the pediatric population to evaluate olanzapine in combination with lithium or valproate for the treatment of manic episodes associated with bipolar disorder (see **SUMMARY OF PREVIOUS COMMUNICATIONS** under May 30, 2002, below).

SUMMARY OF PREVIOUS COMMUNICATIONS

Please refer to the following relevant communications between the Agency and Eli Lilly and Company regarding this application for Zyprexa:

February 20, 1997

A summary of the December 6, 1996 telephone conversation between Dr. Tom Laughren (FDA) and Dr. Gary Tollefson (Lilly) which focused on the clinical plan for registration of olanzapine monotherapy for the treatment of manic episodes associated with bipolar disorder was submitted to IND 28,705. A preliminary description of Protocol HGFU was part of that conversation.

May 15, 1997

A briefing document to support a pre-NDA meeting for the registration of olanzapine monotherapy for the treatment of manic or mixed episodes associated with bipolar disorder was submitted to IND 28,705. Protocol HGFU was summarized within this briefing document indicating that the study would start prior to submission of the supplemental NDA, but would not be part of the submission.

October 27, 1998

Protocol HGFU was summarized in a briefing document submitted to NDA 20-592 to support a meeting with the Division regarding further understanding of the FDA's position on issues described in the October 2, 1998 not approvable letter for NDA 20-592

S006 (olanzapine monotherapy for the treatment of manic or mixed episodes associated with bipolar disorder).

February 9, 2000

A briefing document summarizing Lilly's proposed bipolar disorder clinical plan, including the registration of the use of Zyprexa in combination with lithium or valproate, was submitted to IND 28,705 to support the February 23rd meeting.

February 23, 2000

A meeting was held between representatives of Lilly and the Agency to discuss Lilly's proposed bipolar disorder clinical plan, including the registration of the use of Zyprexa in combination with lithium or valproate. The Division indicated that achieving positive results in a single study evaluating the efficacy of olanzapine compared with placebo when each is added to lithium or valproate would be adequate for an adjunctive therapy acute mania claim.

March 16, 2000

Lilly's minutes of the February 23, 2000 meeting were submitted to IND 28,705.

May 14, 2002

A briefing document supporting the May 30, 2002 pre-NDA meeting was submitted to IND 28,705.

May 30, 2002

A pre-NDA meeting was held between representatives of Lilly and the Agency to discuss Lilly's planned supplemental NDA to support the approval of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes. The following agreements were reached during the meeting:

- 1) The Division agreed with the proposed content and format of the submission table of contents. Additionally, the Division agreed that an application summary, ISE, ISS and electronic Assay folder were not necessary.
- 2) The Division agreed that a study in pediatric patients evaluating olanzapine in combination with mood stabilizers in the treatment of bipolar mania would not be required and thus a pediatric waiver could be obtained.
- 3) The Division agreed that patient narratives should be provided for all patients who died, experienced a serious adverse event, discontinued due to adverse event, experienced other clinically significant adverse events defined as potentially clinically significant (PCS) low neutrophils, PCS low white blood counts, PCS QTc Bazett's formula and any other event determined by Lilly physician. The Division requested that the proposal to include patient narratives for patients who experience clinically significant adverse events defined as PCS high glucose abnormalities (> 250 mg/dL) should be changed to > 200 mg/dL. Additionally, the Division requested that patient narratives for patients who experience treatment-emergent diabetes where an oral antidiabetic agent or insulin is prescribed or patients who experience an exacerbation of diabetes where existing

treatment with an oral antidiabetic agent is changed to insulin therapy be included in the submission.

4) The Division agreed that case report forms for patients who died, discontinued due to adverse events, and reported serious and unexpected adverse events should be included in the submission.

5) The Division agreed that the clinical pharmacology study HGGB does not meet the "covered study" definition for financial disclosure and thus only financial disclosure information from Protocol HGFU would be included in the submission.

June 10, 2002

Lilly's minutes of the May 30, 2002 meeting were submitted to IND 28,705.

June 21, 2002

Lilly received e-mail message from Mr. Randy Levin (FDA) confirming agreement with electronic format proposed in briefing document submitted May 14, 2002.

July 8, 2002

Lilly received official minutes from FDA for the May 30, 2002 meeting.

SUBMISSION INFORMATION

This supplemental NDA is submitted in electronic format according to the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs," also referred to as the Electronic Submissions Guidance. As specified in this guidance and per agreements reached with Dr. Randy Levin via e-mail correspondence, a paper copy of the submission is submitted as a review copy. In order to add clarification and perspective, the following comments are being made (in FDA Form 356H format) for this supplemental NDA.

Cover Letter

Sponsor contact information is provided in the cover letter.

Items 1-2 (NDA Table of Contents, Labeling)

These two items are contained within Volume 1 of the submission. A copy of the annotated and unannotated proposed labeling text is included in Item 2.

In addition, Items 13, 14, 16, 18, 19, and 20 (patent information and certification, debarment certification, user fee cover sheet information, financial disclosure information and request for pediatric waiver) are also contained within Volume 1 of the submission.

In the current approved Zyprexa labeling, revised labeling text is proposed in the following sections: CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION. Revised labeling text supported by results from Protocols HGFU and HGGB are

annotated by electronic links to these clinical study reports included in this submission. The rationales for additional revised labeling text are as follows:

Under the *Clinical Efficacy Data* subsection of CLINICAL PHARMACOLOGY, the revised labeling proposes parenthetical inclusion of the symptoms corresponding to the 11 items from the Young Mania Rating Scale (Y-MRS), the primary efficacy scale in Protocol HGFU. Since launch of the bipolar mania monotherapy indication in April 2000, we have come to learn that prescribing clinicians are not as familiar with the Y-MRS as previously thought and thus we believe that inclusion of these symptoms would serve to further educate the prescribers.

Under the *Drug Interactions* subsection of PRECAUTIONS, the revised labeling proposes moving the currently approved reference of the results from the lithium clinical pharmacology study (E001; submitted September 21, 1995 with NDA 20-592) to its own sub-heading under this section. With the proposed registration of the use of olanzapine in combination with lithium or valproate, the new subheading would allow the reader to more easily find the pertinent interaction information.

Under the *Incidence of Adverse Events in Short-Term, Placebo-Controlled Trials* subsection of ADVERSE REACTIONS, the revised labeling proposes re-formatting the currently approved Commonly Observed Adverse Event tables for schizophrenia and bipolar mania into text. This formatting would be consistent with all other currently approved atypical antipsychotic labeling and would continue to convey pertinent safety information in labeling.

Item 3 (Application Summary)

Not applicable to this submission.

Item 4 (Chemistry, Manufacturing and Control)

CM&C information is provided by cross-reference to NDA 20-592.

Item 5 (Nonclinical Pharmacology and Toxicology)

Pertinent nonclinical pharmacology information is provided by cross-reference to NDA 20-592.

Item 6 (Human Pharmacology and Bioavailability/Bioequivalence)

One clinical pharmacology study (HGGB), Olanzapine – Divalproex sodium/Valproic Acid Interaction Trial, is included in this submission. A second pertinent clinical pharmacology study (E001), Pharmacokinetic Interaction Study between Olanzapine and Lithium, Given Orally, after Single and Repeated Administration of Olanzapine in Healthy Volunteers, is provided by cross-reference to NDA 20-592.

Item 7 (Microbiology)

Not applicable to this submission.

Item 8 (Clinical/Statistical)

The clinical study report for the two adequate and well-controlled clinical studies conducted in bipolar patients who displayed acute manic or mixed episodes provide the pivotal data supporting the use of Zyprexa in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder.

The efficacy and safety results from these two acute phase studies conducted under one protocol (F1D-MC-HGFU: Olanzapine Added to Mood Stabilizers in the Treatment of Bipolar Disorder) are provided in a single acute phase clinical study report. Results from the 18-month extension phase of Protocol HGFU is provided in a separate clinical study report intended to provide additional patient safety data supporting the application.

By agreement with FDA during the May 30, 2002 pre-NDA meeting (see **SUMMARY OF PREVIOUS COMMUNICATIONS** under May 30, 2002), the criteria used to identify events requiring patient narratives was modified from criteria used previously in olanzapine NDAs and efficacy supplements in order to more accurately identify clinically informative cases for the preparation of patient narratives and reduce the submission of uninformative patient narratives. Because both the HGFU acute and extension phase clinical study reports were already completed prior to the May 30, 2002 pre-NDA meeting, all narratives completed with the original HGFU study reports are included with those study reports. The additional patient narratives prepared for any events that met the revised criteria that were not already included in the study report are provided as a separate document in Item 8.

As agreed during the May 30, 2002 meeting (see **SUMMARY OF PREVIOUS COMMUNICATIONS** under May 30, 2002), a separate Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS) are not applicable to this submission.

Item 9 (Safety Update Report)

A safety update is not applicable at this time.

Item 10 (Statistical)

This item is the same as Item 8, and is therefore not duplicated.

Item 11 (Case Report Tabulations)

Case Report Tabulations are provided by electronic media only, and are not included in the paper review copy. The electronic version of the supplemental NDA contains datasets for Studies HGFU and HGGB. The format of the electronic datasets and accompanying documentation conform to the Guidance for Electronic Submissions. The HGGB datasets in this submission do not currently include the pharmacokinetic datasets. The pharmacokinetic datasets will be provided by electronic media prior to the 45-day filing date.

Item 12 (Case Report Forms)

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Case Report Forms (CRFs) are provided by electronic media only. No paper copies of CRFs will be submitted in the paper review copy of this supplemental NDA.

Item 12 contains scanned images of CRFs for all patients who died, discontinued due to adverse events, and reported serious and unexpected adverse events. The CRFs are submitted in the Adobe Portable Document Format as specified in the Electronic Submissions Guidance.

Item 13 (Patent Information)

Patent information is provided.

Item 14 (Patent Certification)

Patent certification is provided.

Item 15 (Establishment Description)

Not applicable to this submission

Item 16 (Debarment Certification)

A copy of the debarment certification is provided.

Item 17 (Field Copy Certification)

Not applicable to this submission.

Item 18 (User Fee Cover Sheet)

A user fee of \$156,660 has been paid under User Fee ID Number 4411. A check for this amount has been sent to the Mellon Bank, Pittsburgh, Pennsylvania.

Item 19 (Financial Disclosure)

Information related to Financial Interests and Arrangements of Clinical Investigators is provided (FDA Form 3454). As agreed during the May 30, 2002 pre-NDA meeting (see **SUMMARY OF PREVIOUS COMMUNICATIONS** under May 30, 2002), this information pertains to the clinical investigators for the HGFU study.

Item 20 (Pediatric Waiver)

A request for pediatric waiver is included in Item 20.

MINUTES OF MEETING WITH FIRM
Olanzapine (Bipolar Disorder), IND 28,705
Eli Lilly and Co.
Pre-sNDA Meeting

DATE: May 30, 2002 (8:30 – 10:00 A.M.)

LOCATION: WOC II Conference Room

PARTICIPANTS: *LILLY:* R. Baker, G. Brophy, M. Namjoshi, R. Risser, M. Sharp, M. Tohen, D. Williamson

FDA: R. Katz, T. Laughren, P. Andreason, J. Racoosin, K. Jin, O. Siddiqui, R. Baweja, D. Bates

Background: Olanzapine is presently approved as an antipsychotic and for treatment of acute manic / mixed episodes associated with bipolar disorder. Lilly has been studying this chemical entity, both as maintenance therapy in bipolar disorder and as adjunctive therapy with lithium or valproate) in the treatment of bipolar mania.

Following a meeting on April 30, 2002 in which both the single entity and combination with fluoxetine were discussed in the treatment of bipolar depression, this meeting was requested in order to discuss the submission of supplements for olanzapine in the indications and treatment modalities cited above. A briefing book was received by the Agency on May 14 2002.

Discussion: The discussion is presented point-by-point, following the order of the questions in the briefing book. For background on each question, please refer to the briefing book. Note: Questions 1 – 8 refer to the bipolar disorder maintenance indication. A second set of questions refers to the bipolar mania combination therapy indication and is addressed by reference to the maintenance discussion, with inclusion of points unique to the combination / mania indication. The slides presented by Lilly are included with these minutes as an attachment, prior to the electronic signature page.

[Bipolar Maintenance] Discussion began with a presentation of the design of pivotal study HGHL. Dr. Racoosin advised Lilly that information on prior medication history will be highly relevant for classifying treatment-emergent Serious Adverse Events (SAEs).

Question 1a. *Does the Division agree with the proposed draft labeling strategy (i.e., sections anticipated to be revised)?*

FDA Response. Dr. Katz explained that the strategy was acceptable as a starting point, but the actual language and any additional modifications to labeling would be a matter of review.

1b. *Does the Division agree that the proposed statistical analysis plan for Protocol F1D-MC-HGHL (as described in Section 3.5.1.) supports the proposed indication?*

FDA Response. Dr. Siddiqui asked how many (%) of patients would be expected to remain in the study for 12 months. Lilly estimates ca. 50%. Dr. Siddiqui then indicated that the study would fail to be a 12 month study if patient attrition (ADOs, treatment failures) is sufficiently significant prior to this time point. However, the Division did not indicate any specific issues with the analysis plan *per se*. Again it was noted that the primary statistical evaluation would occur during the review process.

1c. *Since positive results in a single study (F1D-MC-HGHL) are sufficient to obtain the maintenance indication, does the Division agree that positive results in the proposed sequential*

testing of secondary efficacy measures in the same study are also sufficient to permit inclusion of these measures in labeling?

1d. Does the Division agree that the five secondary efficacy measures (SF-36 role limitations due to physical problems dimension, SLICE/LIFE work activity impairment question, SLICE/LIFE household activity impairment question, SF-36 social functioning dimension, and SF-35 role limitations due to emotional problems dimension) that we are now proposing, prior to data lock, are acceptable measures to be included in labeling?

FDA Response. Both questions were discussed together. Dr. Katz explained that since only one study will be performed, the issue of replication of findings arises; for secondary outcomes to be included in labeling, they must be prospectively declared, agreed upon, and replicated. The issue of pseudospecificity and overlapping domains for the rating scales was also noted as a potential problem (as well as the fact that the Division is unfamiliar with the SLICE/LIFE scales).

With respect to specificity, Lilly clarified that these secondary scales were used in earlier, acute studies, but were not prospectively designated therein. HGFU does not include them, although the lithium combination study does. FDA indicated that the lithium study results might be useful in this respect, provided that olanzapine showed clear superiority to lithium on both primary and secondary outcome measures. Noninferiority alone would not suffice.

With respect to overlapping domains, FDA noted that the various scales look like segments of a global functionality scale and the subdivision of such a global scale is questionable. The Division recommended that a global functionality rating scale be selected to avoid redundancy. Again, as for the issue of specificity, noninferiority would not suffice for results from earlier trials to be usable in support of these secondary outcomes. Superiority would need to be demonstrated, first for the primary outcome, then for the secondaries.

An issue related to possible missing data was resolved by clarification of timepoints for performing the SF-36. FDA was satisfied that this rating was performed sufficiently frequently per study design to avoid a missing data problem.

1e. Does the Division agree with the proposed strategy for presentation of safety information under the ADVERSE REACTIONS Section?

FDA Response. The proposed strategy is acceptable for the 'laundry list' of adverse events, but should not be used if any new AE is identified.

1f. Does the Division agree with the proposed strategy for handling analysis of adverse events in Coding Symbol and Thesaurus for Adverse Event Terminology (COSTART) and Medical Dictionary for Regulatory Activities (MedDRA) within the submission documents and subsequent incorporation of overall safety information into the label as described in Section 3/10?

FDA Response. The Division recommended that Lilly avoid performing the AE analysis in one coding language while continuing to present labeling in another. There was discussion of 'sorting losses' (i.e., differences in terminology resulting in apparent dilution of AEs such as tachycardia) when switching to MedDRA.

Question 2.a. *Does the Division agree that the proposed statistical analysis plan for the HGHL Clinical Study Report is acceptable?*

FDA Response. Yes.

2b. *Does the Division agree that the proposed statistical analysis plan for the HGHT Clinical Study Report is acceptable?*

FDA Response. Yes.

2c. *Does the Division agree that the plans as outlined for the ISE and ISS are acceptable and appropriate to support the anticipated revisions of labeling for olanzapine?*

FDA Response. It was noted that the studies HGHT and HGHL are fundamentally different in design and not combinable for safety data analysis. Dr. Racoosin asked whether any studies included patients who were naïve to olanzapine; Lilly clarified that the valproate study would include such patients. It was also clarified that for studies HD and EH (table 3.8, p.58) data would be provided from the open-label portion of the study, not baseline. For the pivotal trial, the deaths, ADOs, and SAEs will be analyzed statistically. Finally, Dr. Racoosin requested person-time exposure information along with mean and modal dose data, which Lilly agreed to provide. This person-time should include time on open-label drug as well, and be presented separately for each trial / database.

With respect to potentially clinically significant events, orthostatic HT greater than or equal to 20 mm HG combined with an increase in bpm of 10 or more should be included. It was clarified that the threshold for reporting weight increase remains at 7%, and that weight decrease will also be reported, to the same threshold. Finally, Dr. Racoosin noted that FDA will analyze transaminases using a cutoff of three times the upper limit of normal.

The ISE proposal was acceptable as presented.

2d. *Does the Division agree that it is acceptable to exclude data from Protocol F1D-MC-HGGW from the proposed submission?*

FDA Response. Yes, except that deaths, SAEs, and ADOs should be included. In a post-meeting communication, Lilly proposed including a summary of the findings from this study for all patients with deaths, SAEs, and ADOs, plus the accompanying patient narratives for all patients in these categories who were receiving olanzapine. This information would be provided in a separate section rather than as part of the ISS, and would not be integrated into the overall safety database. Clinical study reports would not be included. Dr. Racoosin found this proposal acceptable, but in addition requested that Lilly calculate the frequency of SAEs and discontinuation due to AEs by treatment group. This request was agreed to by the firm.

Question 3. *Would the Division confirm that a study in pediatric patients evaluating the use of olanzapine in maintaining a response in bipolar disorder would not be required?*

FDA Response. The Division agreed to grant a waiver for this study / indication.

Question 4.a. *Does the Division agree with the criteria for identifying the patient narratives to be included in this submission?*

FDA Response. Dr. Racoosin noted that hyperglycemia is an issue that the Division is looking at more closely, and requested that Lilly set a limit for blood glucose of 200 mg/dL or higher for inclusion of narratives. Similarly, any patient who is diagnosed with diabetes during the trial and enters treatment, or known diabetic patients whose treatment is modified, including a change from oral hypoglycemic drugs to insulin therapy, should be included in the narratives.

Otherwise, FDA was in agreement with the proposals.

4b. Does the Division agree with the criteria for identifying the case report forms to be included in this submission?

FDA Response. Yes.

Question 5a. Does the Division agree that the proposed Table of Contents of the anticipated sNDA provides the appropriate content to support registration of olanzapine for the maintenance of treatment response in bipolar disorder?

FDA Response. Yes.

5b. Does the Division agree that the proposed table of Contents of the anticipated sNDA is appropriately structured?

FDA Response. Yes.

5c. Does the Division agree that an application summary is not necessary for this sNDA?

FDA Response. Yes.

Question 6. Does the Division agree that a 4-month safety update consisting of the HGGY open-label extension abbreviated clinical study report and updated ISS tables for deaths, serious adverse events, discontinuations due to adverse events, and treatment-emergent adverse events from the Overall Integrated Database is appropriate?

FDA Response. Yes.

Question 7a. Does the Division have any specific requests regarding the electronic submission?

FDA Response. This area will be discussed between Dr. Randy Levin of FDA and Lilly personnel.

7b. Are there any portions of the paper review copy (technical sections) that the Division would like to eliminate from the submission?

FDA Response. Division reviewers have mixed preferences; information should be provided as described in the Guidance (per Dr. Levin) and if review aids are needed they can be requested subsequently where appropriate.

Question 8. Are there issues that the Division feels Lilly has not addressed but should address as part of the sNDA submission?

FDA Response. No issues were prospectively identified. Lilly indicated that this application will probably be submitted to the Agency during the 4th quarter of 2002.

[Bipolar Mania Combination Therapy: Olanzapine plus lithium or valproate]

For this discussion, the questions were essentially the same as those for the maintenance therapy application. The Division noted that responses would be the same as those discussed above. FDA inquired about the status of study HGFU as non-pivotal; the firm explained that this study did not achieve statistical significance when evaluated for prevention of depressive episodes (syndromatic evaluation), although it did so when evaluated for either time to relapse or prevention of manic episodes.

A similar pediatric waiver was granted for this application. Lilly indicated that this submission would probably be made in September 2002.

PLEASE SEE ELECTRONIC SIGNATURE PAGE. DRS. BATES AND LAUGHREN ARE SIGNING THESE MINUTES FOR THE ATTENDEES; DR. KATZ WILL SIGN THEM TO INDICATE THEIR ACCEPTANCE FOR DIVISION INTERNAL RECORDS AND FOR EXTERNAL RELEASE.
NOTE: ELECTRONIC SIGNATURES WILL APPEAR ON LAST PAGE OF DOCUMENT, FOLLOWING ALL SLIDES.

Doris J. Bates, Ph.D.
Regulatory Project Manager

Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drugs Group

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Doris Bates
6/26/02 04:20:15 PM

Thomas Laughren
6/30/02 12:42:11 PM

Russell Katz
7/2/02 11:07:27 AM

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information from

Administrative *Correspondence
Minutes of Meeting with Firm (5/30/02)