

Clinical Review
 Cara Alfaro, Pharm.D.
 NDA 20-592 S-040
 Zyprexa (olanzapine)

Overall Combined Database

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIN-019-1901	SUICIDAL IDEATION / SUICIDAL IDEATION	4	167	No
HGIN-026-2603	SUICIDAL IDEATION / SUICIDAL IDEATION	4	135	No
HGIN-030-3001	SUBJECT IS EXPERIENCING SYMPTOMS OF DELUSIONS, AUDITORY AND VISUAL HALLUCINATIONS, AND SUICIDAL IDEATIONS SUBJECT WILL BE HOSPITALIZED FOR STABILIZATION ON TRADITIONAL MEDICATION	4	51	No
HGIN-930-9307	SUICIDE ATTEMPT / SUICIDE ATTEMPT	2	59	No
HGIU-001-0108	ALCOHOL POISONING / ETOH INTOXICATION. LSS: ON (b) (6), NEARLY SIX MONTHS AFTER STARTING STUDY DRUG, THE PATIENT WAS ADMITTED TO THE HOSPITAL WITH ALCOHOL ("ETOH") POISONING. THE PATIENT WAS RECEIVING 15MG OLANZAPINE AT THE TIME OF THE EVENT. THIS WAS THE FIRST PSYCHIATRIC HOSPITALIZATION FOR THIS 14-YEAR OLD WHO WAS BROUGHT TO THE EMERGENCY ROOM (ER) BY POLICE AFTER THE PATIENT BECAME INTOXICATED, VOICED SUICIDAL IDEATION, AND PASSED OUT AT SCHOOL. APPROXIMATELY (b) (6) (A WEEK AND A HALF A GO), THE PATIENT TRIED TO JUMP OUT OF HER MOTHER'S MOVING VEHICLE AT 55 MILES PER HOUR, BUT THE MOTHER PREVENTED HER FROM FALLING OUT.	3	157	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
HGIU-012-1206	INTENTIONAL SELF-INJURY / SELF-IMPLICATED CUT MARKS ON FOREARM	5	22	No
HGIU-012-1211	SUICIDAL IDEATION / SUICIDAL IDEATION	4	14	No
HGIU-012-1212	THE PATIENT HAD BEEN DRAWING PICTURES OF HOW THE PATIENT COULD DIE . . . THE PATIENT COULD NOT ASSURE THE INVESTIGATOR THAT SHE WOULDN'T HARM HERSELF.	4	34	No
HGIU-013-1301	SUICIDAL IDEATION / OCCASIONAL SUICIDAL THOUGHTS	4	71	No
HGIU-013-1310	INTENTIONAL SELF-INJURY / SELF INJURY	5	64	No
HGIU-020-2016	SUICIDE ATTEMPT / ATTEMPTED SUICIDE	2	214	No
HGIU-026-2604	SELF INJURIOUS BEHAVIOUR / SELF-INJURIOUS BEHAVIOR. LSS: THE PATIENT REPORTED THAT HIS DEPRESSION WORSENEED APPROXIMATELY ONE WEEK PRIOR (b) (6). ADDITIONALLY HE BEGAN FEELING SUICIDAL (WITHOUT PLAN) APPROXIMATELY THREE DAYS PRIOR (b) (6). THE PATIENT'S MOTHER CALLED THE SITE TO REPORT THAT THE PATIENT HAD CUT HIMSELF THE PRIOR EVENING AND DIDN'T FEEL SAFE. THE PATIENT WAS BROUGHT TO THE HOSPITAL FOR SAFETY AND STABILIZATION.	4	59	No

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HGIU-026-2605	THE PATIENT WAS BEHAVING INAPPROPRIATELY AND WAS ON THE ROOF OF HIS HOME REFUSING TO COME DOWN	9	53	No
HGIU-026-2605	SUICIDAL IDEATION / SUICIDAL IDEATION	4	35	No
HGIU-027-2705	INTENTIONAL SELF-INJURY / SELF-INFLICTED SUPERFICIAL LACERATIONS	5	76	No
HGIU-028-2805	SUICIDAL IDEATION / SUICIDAL IDEATION. LSS: THE PATIENT'S MOTHER CALLED THE INVESTIGATOR'S SITE ON 14-MAY-2004 TO STATE THAT HER DAUGHTER HAD BECOME SUICIDAL WITH A PLAN TO OVERDOSE ON LORAZEPAM (ATIVAN) DURING THE LAST WEEK OF MAY 2004, BUT ENDED UP TELLING HER PARENTS THE EVENING OF 09-MAY-2004.	3	108	No
HGIU-730-7302	SUICIDAL IDEATION / PASSIVE SUICIDAL IDEATION	4	177	No
HGMP-003-0304	EXACERBATION OF BIPOLAR ILLNESS WITH POSITIVE SUICIDAL IDEATION	4	29	No
HGMP-008-0805	INTENTIONAL SELF-INJURY, CUTTING LEFT ARM	5	93	No
LOAY-400-4001	PATIENT IS IN A DEPRESSIVE MOOD AROUND 10-11.05.99 AND EXPRESSES SUICIDAL THOUGHTS, SIGNIFICANTLY SLOWED MOVEMENT.	4	44	No
LOAY-401-4012	SELF-INJURIOUS BEHAVIOR, SELF-INJURY	5	16	No
LOAY-407-4077	SELF INJURIOUS BEHAVIOR, SELF-INFLICTING TENDENCIES	5	55	No

Patient ID (Study-Inv-Patient)	Brief Description of Event	Code	Days to Event	Fatal?
LOAY-407-4078	SUICIDAL IDEATION, ACUTE SUICIDAL TENDENCIES	4	4	No
LOAY-413-4150	SUICIDAL IDEATION, SUICIDAL TENDENCY	4	27	No

10.9 Laboratory Evaluations – Mean Change from Baseline to Endpoint

Table 10.9.1 Sponsor's Table. Mean Change from Baseline to Endpoint: HGIN + HGIU Acute Database

Table 2.7.4.33. Laboratory Evaluations
 Mean Change from Baseline to Endpoint
 Acute Placebo-Controlled Combined Database

Laboratory Evaluations	Unit	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
				Mean	Std	Mean	Std			
HEMATOCRIT	l	Olz	174	0.43	0.03	-0.01	0.03	-0.01	-0.01	<.001
		Placebo	87	0.43	0.04	-0.00	0.03	-0.00		
HEMOGLOBIN	mmL/L-F	Olz	174	8.93	0.78	-0.30	0.47	-0.30	-0.22	<.001
		Placebo	87	8.93	0.83	-0.08	0.41	-0.07		
ERYTHROCYTE COUNT	TI/L	Olz	174	5.00	0.39	-0.15	0.27	-0.15	-0.11	.002
		Placebo	87	4.99	0.49	-0.04	0.26	-0.04		
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	mmL/L-F	Olz	174	20.87	0.92	-0.00	0.76	0.02	0.16	.100
		Placebo	87	21.80	0.79	-0.17	0.73	-0.14		
LEUCOCYTE COUNT	GI/L	Olz	174	7.27	1.92	-0.19	1.86	-0.10	-0.32	.201
		Placebo	87	7.18	1.91	0.14	1.99	0.21		
NEUTROPHILS, SEGMENTED	GI/L	Olz	174	4.22	1.59	-0.13	1.67	-0.06	-0.29	.203
		Placebo	87	4.29	1.48	0.17	1.79	0.23		
LYMPHOCYTES	GI/L	Olz	174	2.38	0.66	-0.09	0.49	-0.06	-0.07	.297
		Placebo	87	2.24	0.60	-0.02	0.51	0.01		
MONOCYTES	GI/L	Olz	174	0.43	0.14	0.02	0.17	0.01	0.01	.544
		Placebo	87	0.41	0.16	0.01	0.17	0.00		

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Laboratory Evaluations	Unit	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
				Mean	Std	Mean	Std			
EOSINOPHILS	GI/L	Olz	174	0.20	0.21	0.01	0.16	0.01	0.04	.042
		Placebo	87	0.19	0.14	-0.02	0.10	-0.03		
BASOPHILS	GI/L	Olz	174	0.05	0.03	-0.01	0.03	-0.01	-0.01	.008
		Placebo	87	0.05	0.03	0.00	0.03	0.00		
MEAN CELL VOLUME (MCV)	fL	Olz	174	85.96	4.66	-0.25	2.53	-0.02	-0.97	.005
		Placebo	87	85.76	4.59	0.72	2.78	0.95		
PLATELET COUNT	GI/L	Olz	173	291.08	68.65	1.26	46.42	1.44	6.09	.339
		Placebo	87	286.54	63.84	-4.68	52.18	-3.66		
LYMPHOCYTES, ATYPICAL	GI/L	Olz	1	0.06		0.03		0.03		
UA-SPECIFIC GRAVITY	NO UNIT	Olz	156	1.02	0.01	-0.00	0.01	-0.00	-0.00	.282
		Placebo	72	1.02	0.01	-0.00	0.01	-0.00		
AST/SGOT	U/L	Olz	175	24.53	29.87	6.43	26.41	9.89	8.91	.002
		Placebo	87	23.63	8.46	-2.47	7.51	0.98		
ALT/SGPT	U/L	Olz	175	24.13	45.95	19.95	54.84	28.11	22.98	<.001
		Placebo	87	20.39	13.05	-3.08	11.69	5.13		
CREATINE PHOSPHOKINASE	U/L	Olz	175	141.28	138.78	-7.31	131.11	2.81	16.06	.376
		Placebo	87	164.36	160.04	-23.62	152.22	-13.25		

Laboratory Evaluations	Unit	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
				Mean	Std	Mean	Std			
ALKALINE PHOSPHATASE	U/L	Olz	175	152.33	32.35	-1.35	25.61	-2.74	2.57	.396
		Placebo	87	138.67	86.92	-3.97	16.63	-5.31		
GGT (GGPT/SGGT/IGGT)	U/L	Olz	175	18.99	12.31	7.47	20.02	7.73	7.89	<.001
		Placebo	87	17.68	8.49	-0.43	5.96	-0.16		
THYROID STIMULATING HORMONE	mU/L	Olz	6	2.73	2.32	0.11	1.02	-0.12		
UREA NITROGEN	mmol/L	Olz	175	4.40	1.18	0.22	1.18	0.14	0.39	.610
		Placebo	87	4.37	1.06	-0.17	1.06	-0.25		
CREATININE	umol/L	Olz	175	93.29	14.47	-2.90	9.85	-2.07	-1.80	.147
		Placebo	87	95.83	12.43	-1.08	8.56	-0.27		
CALCIUM	mmol/L	Olz	175	2.48	0.08	-0.03	0.09	-0.03	-0.02	.215
		Placebo	87	2.50	0.12	-0.01	0.10	-0.02		
SODIUM	mmol/L	Olz	175	141.70	2.27	-0.05	2.83	-0.12	0.49	.190
		Placebo	87	141.73	2.44	-0.53	2.94	-0.61		
POTASSIUM	mmol/L	Olz	175	4.32	0.33	-0.04	0.36	-0.07	0.04	.462
		Placebo	87	4.41	0.42	-0.07	0.41	-0.10		
ALBUMIN	g/L	Olz	175	45.07	3.75	-2.01	3.20	-2.13	-1.70	<.001
		Placebo	87	45.39	3.03	-0.31	2.90	-0.43		

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Laboratory Evaluations	Unit	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
				Mean	Std	Mean	Std			
GLUCOSE, FASTING	mmol/L	Olz	135	4.89	0.55	0.15	0.58	0.15	0.31	<.001
		Placebo	64	4.98	0.57	-0.16	0.56	-0.17		
GLUCOSE, NON-FASTING	mmol/L	Olz	141	5.04	0.83	0.17	1.13	0.12	0.15	.374
		Placebo	73	5.01	0.79	0.03	1.23	-0.03		
URIC ACID	umol/L	Olz	175	331.18	74.27	25.21	51.54	30.87	26.95	<.001
		Placebo	87	329.40	84.01	-1.86	53.02	3.92		
CHOLESTEROL	mmol/L	Olz	175	4.17	0.83	0.34	0.59	0.33	0.37	<.001
		Placebo	87	4.15	0.85	-0.03	0.63	-0.04		
TRIGLYCERIDES	mmol/L	Olz	175	1.18	0.66	0.33	0.91	0.30	0.38	<.001
		Placebo	87	1.25	0.73	-0.05	0.62	-0.07		
LDL CHOLESTEROL	mmol/L	Olz	175	2.42	0.74	0.16	0.52	0.14	0.17	.016
		Placebo	87	2.37	0.76	-0.01	0.53	-0.02		
BILIRUBIN, TOTAL	umol/L	Olz	175	7.84	5.27	-1.73	3.82	-2.21	-2.52	<.001
		Placebo	87	8.56	5.33	0.78	5.96	0.31		
BILIRUBIN, DIRECT	umol/L	Olz	175	1.84	1.07	-0.33	1.07	-0.36	-0.38	.005
		Placebo	87	2.01	1.08	0.05	0.93	0.02		
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Olz	175	1.22	0.31	0.03	0.23	0.02	0.03	.331

Laboratory Evaluations	Unit	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
				Mean	Std	Mean	Std			
HDL CHOLESTEROL-DEXTRAN PRECIP.	mmol/L	Placebo	87	1.21	0.25	-0.00	0.25	-0.01		
PROLACTIN	ug/L	Olz	163	14.06	9.92	11.44	14.52	10.51	11.66	<.001
		Placebo	80	14.95	11.86	-0.16	10.69	-1.15		
HEMOGLOBIN A1C	%	Olz	6	0.05	0.00	-0.00	0.00	-0.00	0.00	.741
		Placebo	3	0.05	0.01	-0.00	0.00	-0.00		

10.10 Prolactin Analysis by Gender

Table 10.10.1. Sponsor's Table. Mean Change from Baseline to Endpoint for Prolactin by Gender: HGIU + HGIN Acute Database.

Laboratory Evaluations	Gender	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value	**P-value
				Mean	Std	Mean	Std				
PROLACTIN	Female	Olz	63	15.87	10.06	15.63	16.96	14.26	14.25	<.001	.236
		Placebo	37	15.25	7.59	1.35	9.20	0.00			
	Male	Olz	100	12.92	9.71	8.80	12.20	8.70	10.12	<.001	
		Placebo	43	14.70	14.67	-1.46	11.78	-1.42			

10.11 Vital Signs – Mean Change from Baseline to Endpoint

Table 10.11.1 Vital Signs, Weight, Height and BMI - Mean Change from Baseline to Endpoint (LOCF). HGIN + HGIU Acute Database

Vital signs	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
			Mean	Std	Mean	Std			
Systolic Blood Pressure - Supine	Olz	177	111.52	10.95	2.94	10.57	1.73	3.66	.009
	Placebo	89	112.79	13.18	-0.71	10.90	-1.93		
Systolic Blood Pressure - Standing	Olz	177	113.33	12.25	3.14	12.06	2.16	1.94	.225
	Placebo	89	112.18	13.25	1.22	12.51	0.23		
Systolic Blood Pressure - Orthostatic	Olz	177	-1.81	9.63	-0.20	11.68	-0.43	1.72	.262
	Placebo	89	0.61	8.33	-1.93	11.83	-2.15		
Diastolic Blood Pressure - Supine	Olz	177	67.71	9.27	1.24	9.74	1.56	2.17	.095
	Placebo	89	68.19	8.53	-0.92	10.27	-0.61		
Diastolic Blood Pressure - Standing	Olz	177	72.86	10.12	1.42	10.25	-0.24	2.73	.033
	Placebo	89	73.56	9.48	-1.28	9.14	-2.97		
Pulse - Supine	Olz	177	73.88	11.40	7.07	13.99	7.55	7.71	<.001
	Placebo	89	74.15	12.81	-0.60	12.04	-0.16		
Pulse - Standing	Olz	177	83.77	12.73	6.97	14.83	6.55	7.90	<.001
	Placebo	89	85.55	12.98	-0.89	14.69	-1.35		
Pulse - Orthostatic	Olz	177	9.89	11.23	-0.11	13.37	-1.01	0.19	.914
	Placebo	89	11.40	11.15	-0.29	13.09	-1.19		

Vital Signs	Therapy	N	Baseline		Change to Endpoint		LSMean Change	LSMean Difference	*P-value
			Mean	Std	Mean	Std			
Temperature in Centigrade	Olz	177	36.57	0.44	-0.03	0.49	-0.03	-0.03	.695
	Placebo	88	36.58	0.42	-0.00	0.49	-0.00		
Weight in Kg	Olz	177	66.03	17.93	3.90	2.72	3.68	3.66	<.001
	Placebo	88	67.63	17.24	0.24	2.16	0.01		
Height in cm	Olz	177	165.84	10.13	0.48	1.22	0.46	0.18	.235
	Placebo	88	167.59	9.67	0.31	1.01	0.28		
Body Mass Index	Olz	177	23.91	6.01	1.22	1.01	1.11	1.17	<.001
	Placebo	88	23.98	5.67	0.05	0.91	-0.07		

10.12 Potentially Clinically Significant Definitions for Safety Analyses

Table 2.7.4.6. Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs and Weight

Parameter	Low	High
Orthostatic hypotension (mm Hg)	≥20 mm Hg decrease in systolic BP (supine to standing) and ≥10 bpm increase in pulse (supine to standing)	--
Supine systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Standing systolic BP (mm Hg)	≤90 and decrease ≥20	≥180 and increase ≥20
Supine diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Standing diastolic BP (mm Hg)	≤50 and decrease ≥15	≥105 and increase ≥15
Supine pulse (bpm)	≤50 and decrease ≥15	>120 and increase ≥15
Standing pulse (bpm)	≤50 and decrease ≥15	>120 and increase ≥15
Temperature (°F) ³	--	≥101°F and increase ≥2
Weight (kg)	decrease ≥7%	increase ≥7%

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10.13 Postmarketing Reports - Fatalities
 Table 10.13.1. Postmarketing Reports – Fatalities

Patient Identifier	Date of Death	Dose/Duration	Event	Concom Rx	Comments
BR200605002130 16 YOM	(b) (6)	7.5 mg 10/05 - (b) (6)	Sudden death, cardiac arrest, prescribed overdose, suicide attempt, depression, psychosis	Alprazolam	Brazil Autopsy done, result will be available by June 2006 (per summary)
BE200602002031 17 YOF	(b) (6)	Unknown ~6 years	Bilateral pneumonia, gastric hemorrhagia, fever, coma	Not reported	Belgium (no autopsy)
US_0510123183 14 YO	(b) (6)	Unknown	Toxic exposure, completed suicide	Fluoxetine Risperidone	Literature
JP_051007889 17 YOM	(b) (6)	5 mg, 8/2005 – (b) (6)	Completed suicide, suicidal ideation, apathy	Lorazepam	Japan “Police told psychiatrist about patient’s death, no details provided” [prior suicide attempt per hx]
CA_050708496 17 YOM	(b) (6)	15 mg 11/03 – (b) (6)	Completed suicide	Lorazepam Flupentixol decanoate	Canada 5 days after discontinuing olanzapine, committed suicide (method unknown) Not known whether autopsy performed.
US_0506118439 17 YOF	Unknown (b) (6) estimated	Unknown, 7/1999 - 2004	Death, weight increased, diabetes mellitus, hyperglycemia, multiple drug overdose, triglycerides increased, cholesterol abnormal, musculoskeletal chest pain		Reported by attorney via legal department
EWC050644285 17 YOF	(b) (6)	5 mg 3/5/05 – (b) (6)	Endotoxic shock, kidney infection, sepsis, acute abdomen, disseminated intravascular blood coagulation, myeloid hyperplasia of spleen, pancreatitis, gastric		Russian Federation

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			ulcer perforation, peritoneal infection		
US_0506118189 15 YOM	Unknown (b) (6) estimated	~ May 2003 - unknown	Death		Reported by an attorney via the legal department Cause of death not provided
CA_050207717 16 YOM	(b) (6)	Unknown	Completed suicide	Isotretinoin mepha	Canada No details provided
US_0412108962 16 YOM	Unknown (b) (6) estimated	1-2002 – unknown	Death, diabetes mellitus		Reported by an attorney via the legal department Cause of death not provided, not known if autopsy performed
JP_041105122 17 YOF	(b) (6)	50 mg 11/10/2004 – (b) (6)	Intentional overdose, completed suicide	Paroxetine, sulpiride, amoxapine, fluvoxamine, flunitrazepam	Japan “Coroner refused to provide any information”
USA040979162 US_0402100550 15 YOM	(b) (6)	10/29/2003?	Death, coma Accidental overdose, drug toxicity, intentional drug misuse	Metronidazole, topiramate, clonazepam	Reported by an attorney via the legal department Case reported in a newspaper “Patient was sold olanzapine by another individual, not prescribed” Olanzapine Cp = 490 ng/ml postmortem
US_0412109585 15 YOF	(b) (6)	11/2000 - unk	Diabetic ketoacidosis, diabetic coma, diabetes mellitus, pain, anxiety, drug ineffective	Methylphenidate, sertraline	Reported to company by an attorney No details provided about the event, unknown if an autopsy was performed
EWC031237179 16 YOM	(b) (6)	5 mg, 11/24/2003 – (b) (6)	Death, pulmonary infarction		Greece Pulmonary infarction per autopsy
USA030742307 13 YOF	(b) (6)	5 mg Unknown	Diabetic ketoacidosis, loss of consciousness, dizziness		Diabetic ketoacidosis per autopsy. No labs provided.
USA030741953 17 YOM	(b) (6)	8/2002 – (b) (6)	Convulsion, heart rate increased	Mixed amphetamine salts, trazodone	Cause of death listed as idiopathic seizure disorder, toxicology screen

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					negative
GBS030413039 17 YOM	(b) (6)	12.5 mg 10/2002 – unk	Completed suicide, sedation, eczema	Risperidone, biperiden	United Kingdom Death by drowning, autopsy did not reveal other significant findings
US_020180581 15 YOM	(b) (6)	20 mg Unknown	Acute asthma		Patient had been in blinded study 3/01 – 9/01 prior [F1D- US-X090]; did not receive olanzapine; taking marketed olanzapine at time of event.
US_010973481 17 YOM	Unknown (received by Sponsor (b) (6))	30 mg Unknown	Prescribed overdose, drug toxicity		No details provided, unknown if autopsy performed
EWC010928155 15 YOM	(b) (6)	10 mg 8/1/2001 – (b) (6)	Death	Dextro- amphetamine	Switzerland Asperger's syndrome Patient drowned while swimming in lake; autopsy unremarkable
CA_010603921 17 YOF	Unknown (received by Sponsor (b) (6))	Unknown	Death	Citalopram, valproate semisodium	Canada Patient "died suddenly", autopsy was completed but not available. "Several attempts at follow-up unsuccessful".
CA_010603802 16 YOM	Unknown (received by Sponsor (b) (6))	10 mg 90 days	Diabetic coma	Valproate sodium Topiramate	Canada No personal history of diabetes. Weight at time of event unknown, labs not provided. "Numerous attempts to obtain follow-up unsuccessful".
US_010566315 16 YOM	(b) (6)	5 mg 730 days	Drug interaction, death, hepatic steatosis	Mixed amphet- Amine salts	Patient found dead. Hepatic steatosis per autopsy, no cause of death provided. Autopsy never provided.
US_010158510 17 YOM	(b) (6)	2.5 mg Unknown	Accidental overdose	Citalopram, trazodone	Patient found dead by family member. Cause of death presumed

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					overdose. Olanzapine Cp = 158 ng/ml.
US_000542556 15 YOM	(b) (6)	Unknown 1998 x 120 days	Necrotizing pancreatitis, diabetes mellitus, increased cholesterol	Carbamazepine, paroxetine	Follow-up in the literature
US_000236591 17 YOM	(b) (6)	22.5 mg Unknown	Overdose, death	Fluoxetine, valproate semisodium, nortriptyline, buspirone, haloperidol, thioridazine	Patient died while being restrained by staff in group home.
US97121702A 14 YOM	(b) (6)	12.5 mg 150 days	Asphyxia, agitation	Haloperidol, sertraline	Became agitated on school bus and was restrained and died. Per coroner, cause of death by mechanical asphyxia due to the restraining position.

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/s/

Cara Alfaro
4/6/2007 10:42:11 AM
PHARMACIST

Ni Aye Khin
4/18/2007 11:20:56 AM
MEDICAL OFFICER

I agree with Dr. Alfaro's recommendation that this application
be considered for non-approval; see memo to file
for additional comments.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020592 / S-035, 039, 040, 041, 049,053, 055

021086 / S-21, 031, 032, 034

021253 / S-037, 039, 043

CHEMISTRY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION
 OFFICE OF NEW DRUG QUALITY ASSESSMENT
 POST-MARKETING EVALUATION
 CMC ASSESSMENT FORM**

APPLICANT: LILLY RES LABS	NDA NUMBER: 018936	DOC TYPE: SE1	SEQ NUMBER: 077	SUBMISSION TYPE: ORIGINAL
PROPRIETARY NAME: PROZAC		ESTABLISHED NAME: FLUOXETINE HYDROCHLORIDE		
DOSAGE FORM: CAP		STRENGTH/POTENCY: 10MG, 20MG	PHARMACOLOGICAL CATEGORY:	
LETTER DATE: 9/28/2006	STAMP DATE: 9/29/2006	PDUFA GOAL DATE: 7/5/2007	SUBMISSION (CHECK ONE) FIRM: PA FINAL: PA	
DIVISION IV BRANCH: VII	OND DIVISION: 130	MANAGED BY: OND	PAL: Brown MEDIA SUBMISSION: Electronic	
SUPPLEMENT PROVIDES FOR: an indication for the use of Symbyax and the co-administration of Zyprexa and Prozac for an indication of Treatment Resistant Depression.				
BUNDLED: This bundle includes the following supplements: 18-936/S-077 (lead), 20-592/S-039, 21-086/S-021, and 21-520/S-012.				
CHANGE CATEGORY: Efficacy Supplement				
LABELING INVOLVED: No	PAT: No		COMPARABILITY PROTOCOL: No	PHASE 4 COMMITMENT:
REVIEW PATH: 6 - OND Multi-Discipline Review				
CONSULTS:				
JUSTIFICATION/COMMENTS: 3/8/2007 - BROWNJA				
1. This bundle includes the following supplements: 18-936/S-077 (lead), 20-592/S-039, 21-086/S-021, and 21-520/S-012. 2. Eli Lilly and Company has claimed a Categorical Exclusion from the requirement for an environmental assessment to support the approval of Symbyax (olanzapine and fluoxetine in combination) and the co-administration of Prozac (fluoxetine) and Zyprexa (olanzapine) for treatment resistant depression. Environmental assessments have previously been submitted to the agency for both olanzapine (NDA 20-592, 21-Sep-1995) and fluoxetine (NDA 20-187, 6-Aug-1993). In these assessments, it was concluded that given their projected use rates, neither of these compounds posed a threat to the aquatic environment. The applicant is requesting a categorical exclusion based on 21 CFR 25.31 (b). Even with the addition of the treatment resistant depression indication, the annual peak sales volumes of olanzapine will still be below 1 part per billion. The applicant's request for a categorical exclusion is granted. 3. There are no CMC changes to the approved labeling for 18-936/S-077 (lead), 20-592/S-039, 21-086/S-021, and 21-520/S-012. 4. From a CMC standpoint, these bundled supplements can be approved.				
PAL ACTION: Recommend approval				
BRANCH CHIEF: James Vidra				

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/s/

Janice Brown
3/8/2007 11:18:32 AM
CHEMIST

Jim Vidra
3/9/2007 11:28:22 AM
CHEMIST

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF NEW DRUG QUALITY ASSESSMENT
POST-MARKETING EVALUATION
CMC ASSESSMENT FORM**

APPLICANT: LILLY	NDA NUMBER: 020592 020592	DOC TYPE: SE5 SE5	SEQ NUMBER: 040 041	SUBMISSION TYPE: ORIGINAL
PROPRIETARY NAME: ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/		ESTABLISHED NAME: OLANZAPINE		
DOSAGE FORM: TAB		STRENGTH/POTENCY: 2.5; 5; 7.5; AND 10 MG		PHARMACOLOGICAL CATEGORY:
LETTER DATE: 10/30/2006	STAMP DATE: 10/31/2006	PDUFA GOAL DATE: 4/30/2007	SUBMISSION (CHECK ONE) FIRM: PA FINAL: PA	
DIVISION IV BRANCH: VII	OND DIVISION: 130	MANAGED BY: OND	PAL: Brown MEDIA SUBMISSION: Electronic	
SUPPLEMENT PROVIDES FOR: fulfillment of FDA's request for pediatric studies. 11/15/06 amendment to includes the Environmental Assessment for both Zyprexa indications and request a waiver from the requirement in the new Physicians Labeling Rule that the Highlights section of labeling in the PLR format be limited to one-half page.				
BUNDLED: No				
CHANGE CATEGORY: Efficacy Supplement				
LABELING INVOLVED: Yes - PI only	PAT: No		COMPARABILITY PROTOCOL: No	PHASE 4 COMMITMENT: Np
REVIEW PATH: 6 - OND Multi-Discipline Review				
CONSULTS: NA				
JUSTIFICATION/COMMENTS: 1/12/2007 - BROWNJA				
1. The applicant has requested a categorical exclusion from submitting an environmental assessment for the use of Zyprexa in the treatment of schizophrenia. The active ingredient in Zyprexa is olanzapine and the expected concentration of olanzapine at the point of entry into the aquatic environment would be (b) (4) or less which is less than 1 part per billion (1µg/L) which qualifies for a categorical exclusion as described in 21 CFR 25.31(b). The applicant has also stated that there are no extraordinary circumstances known to exist for this proposed action. The applicant's request for a categorical exclusion is granted. 2. There are no CMC labeling changes. 3. From a CMC standpoint, this supplement can be approved.				
PAL ACTION: Recommend Approval				
BRANCH CHIEF: James Vidra				

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/s/

Janice Brown
1/17/2007 02:49:46 PM
CHEMIST

Jim Vidra
1/17/2007 03:50:48 PM
CHEMIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020592 / S-035, 039, 040, 041, 049,053, 055

021086 / S-21, 031, 032, 034

021253 / S-037, 039, 043

STATISTICAL REVIEW(S)

Addendum

NDA/Serial Number: 20-592
Drug Name: Olanzapine
Indication(s): Schizophrenia for Adolescents
Applicant: Eli Lilly and Company
Date(s): December 29, 2006
Review Priority: Priority

Biometrics Division: Division of Biometrics I
Statistical Reviewer: Fanhui Kong, PhD
Concurring Reviewers: Peiling Yang, H. M. James Hung

Medical Division: Division of Psychiatry Products
Clinical Team: Cara Alfaro, Mitchell Mathis, Thomas Laughren
Project Manager: Doris J. Bates

1. BACKGROUND

Reference is made to Statistical Review of NDA 20592 submitted to DFS on April 6, 2007.

In this NDA submission, the sponsor conducted 2 pivotal short-term olanzapine studies HGIN and HGIU on adolescent patients, one (HGIU) for the treatment of Mania in Bipolar I Disorder and the other (HGIN) is for the treatment of schizophrenia. These studies were reviewed in the Statistical Review. The primary efficacy endpoint for Study HGIN was the change from baseline to Endpoint of BRPS-C total score and the primary statistical analysis was the ANCOVA procedure using LOCF for missing data. The sponsor provided the efficacy analysis results for LOCF, along with that of OC and MMRM.

In the statistical review that I submitted, with the data sets provided by the sponsor, the corresponding analysis results were also given. They are given in Table 1.

Table 1.1: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Studies HGIN --- ITT Population

	Placebo	Olanzapine
Study HGIN	(N=35)	(N=72)
N (Analysis population)	35	72
N (BPRS-C Total Score)	35	72
Baseline Mean	50.1	50.3
Median change from baseline	-9.3	-19.4
ANCOVA Analysis (LOCF)		
LS Mean change from baseline (SE) ^a	-9.1 (2.73)	-19.3 (1.91)
Difference between LS Means and C.I. ^a	-10.1 (-16.7, -3.5)	
P-value ^a	0.003	
MMRM Analysis		
LS Mean change from baseline (SE) ^b	-23.5 (3.06)	-24.7 (1.70)
Difference between LS Means and C.I. ^b	-1.25 (-8.11, 5.61)	
P-value ^b	0.72	
OC Analysis		
N (BPRS-C Total Score)	15	50
LS Mean change from baseline (SE) ^c	-24.1 (3.35)	-24.4 (1.82)
Difference between LS Means and C.I. ^c	-0.25 (-7.9, 7.4)	
P-value ^b	0.95	

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.

b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.

Note: Negative change in score indicates improvement.

Source: Table 3.7 in Statistical Review

Due to the contradictory results between LOCF, MMRM and OC, I suggested that this study did not support the claim of the effectiveness of Olanzapine on the adolescents with schizophrenia.

2. CORRECTIONS

The MMRM analysis was conducted based on the default variance-covariance structure of Variance Components in SAS software package, which requires the independence between the repeated observations for any subject. In fact, the choice of the variance-covariance structure affects the estimate of treatment effect as well as its significance levels dramatically. Usually, the Unstructured variance-covariance matrix is used for MMRM analysis. In order to see which variance-covariance structure gives a better fit for the data, I applied the MMRM procedure using several different variance-covariance structures and gave the corresponding results along with the AIC values. The AIC values are generally used as a goodness-of-fit criterion of the model. The smaller the AIC value is, the better the model seems to fit the data. These results are depicted in Table 2.1

Table 2.1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIN

Variance-covariance Structure	Placebo	Olanzapine	AIC
Variance Components			
LS Mean change from baseline (SE)	-24.1 (3.13)	-24.5 (1.73)	
Difference between LS Means and C.I.	-0.43 (-6.6, 7.5)		
P-value	0.90		4691
Unstructured			
LS Mean change from baseline (SE)	-12.6 (2.99)	-21.5 (1.97)	
Difference between LS Means and C.I.	-8.9 (-16.0, -1.9)		
P-value	0.015		4055.2
Compound Symmetry			
LS Mean change from baseline (SE)	-17.8 (2.61)	-22.9 (1.60)	
Difference between LS Means and C.I.	-5.1 (-11.1, 0.9)		
P-value	0.10		4353.0
Toeplitz			
LS Mean change from baseline (SE)	-14.3 (2.68)	-21.9 (1.65)	
Difference between LS Means and C.I.	-7.67 (-13.8, -1.5)		
P-value	0.015		4129.0
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-21.7 (2.70)	-24.4 (1.53)	
Difference between LS Means and C.I.	-2.68 (-8.8, 3.4)		
P-value	0.39		4356.0
First Order Auto-regression			
LS Mean change from baseline (SE)	-15.4 (2.71)	-22.3 (1.64)	
Difference between LS Means and C.I.	-7.0 (-13.8, -0.8)		
P-value	0.029		4129.0

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Reviewer

In this analysis, country is not used as a factor in the statistical models since it was not prespecified in the protocol. These results indicate that the Unstructured variance-covariance structure in the statistical model seems to give a better fitting. The significance results derived seem to support the claim that Olanzapine improves placebo in treating the adolescents with schizophrenia. Another important observation is that treatment effect estimates and the corresponding p-values are dramatically different for different choices of variance-covariance structure of the repeated observations. This suggests that the efficacy results derived from this model may not be as stable as we expect. Extra care should be exercised in doing such analyses.

Efficacy analysis for each country. The subgroup analysis with respect to country is considered as exploratory. In Table 2.2, the nominal p-values for the treatment effects at Endpoint using MMRM procedure are provided for each country using the Unstructured variance-covariance structure model.

Table 2.2 Treatment Effect by Country by MMRM Analysis

Country	Placebo	Olanzapine
Russia		
N (Number of patients)	16	34
LS Mean change from baseline (SE)	-5.3 (4.46)	-19.0 (2.73)
Difference between LS Means and C.I.	-13.7 (-23.9,3.3)	
P-value	0.012	
US		
N (Number of patients)	19	35
LS Mean change from baseline (SE)	-18.7 (4.13)	-23.5 (2.89)
Difference between LS Means and C.I.	-4.8 (-14.7, -5.1)	
P-value	0.35	

Recourse: Reviewer

Based on the above results, treatment effects seem to be more evident in Russia than in US. Given similar number of subjects in these two countries, the estimated treatment effect in Russia is 13.7 US while that of US is only 4.8. The data suggests that there was a very small placebo effect in Russia while there was a certain placebo effect in US. Careful investigations might be needed to find why this is the case.

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/s/

Fanhui Kong
4/27/2007 11:50:29 AM
BIOMETRICS

Peiling Yang
4/27/2007 12:04:43 PM
BIOMETRICS

James Hung
4/27/2007 01:54:45 PM
BIOMETRICS



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 20-592
Drug Name: Olanzapine
Indication(s): Schizophrenia for Adolescents
Applicant: Eli Lilly and Company
Date(s): December 29, 2006
Review Priority: Priority

Biometrics Division: Biometrics I (HFD-710)
Statistical Reviewer: Fanhui Kong
Concurring Reviewers: Peiling Yang, H. M. James Hung

Medical Division: Division of Psychiatry Products
Clinical Team: Cara Alfaro, Mitchell Mathis, Thomas Laughrem
Project Manager: Doris J. Bates

Keywords: Olanzapine, Adolescent, Schizophrenia, ANCOVA, LOCF, MMRM

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies between November 2002 and May 2005 in the United States, Russia and Puerto Rico. The primary objectives of the studies were to evaluate the efficacy and safety of olanzapine compared with placebo in the treatment of the adolescents (ages 13 to 17) with schizophrenia (Study HGIN) and in the treatment of the adolescents with Mania in Bipolar I Disorder (Study HGIU). The primary efficacy measures were the change from baseline to Endpoint of the BPRS-C total score (Study HGIN) and the change from baseline to Endpoint of the YMRS total score (Study HGIU).

In the two studies, only Study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. Indeed, the difference between treatment groups only occurred in the patients who dropped out of Period II of the study.

1.2 Brief Overview of Clinical Studies

Two pivotal studies were submitted for the evaluation of the efficacy of olanzapine (2.5 to 20mg/day) in the treatment of adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU). The studies were conducted between November 2002 and May 2005 (26 November 2002 to 29 April 2005 for Study HGIN and 18 November 2002 to 9 May 2005 for Study HGIU) in the United States, Russia and Puerto Rico.

Study HGIN was a Phase IV, multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescent with schizophrenia, with a 6-week acute period conducted in the United States and Russia. The primary objective of this study was to assess the efficacy of olanzapine (2.5 to 20 mg/day) compared to placebo in the treatment of adolescents (ages 13 to 17) with schizophrenia. The primary efficacy measure was the change from baseline to endpoint (up to 6 weeks double-blind treatment) in the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

Study HGIU was a Phase IV, multicenter, randomized, double-blind, placebo-controlled, flexible dose study in adolescents with Mania in Bipolar I Disorder, with an acute double-blind treatment period of 3 weeks in the United States and Puerto Rico. The primary objective was to evaluate the efficacy and safety of olanzapine (2.5 to 20mg/day) compared with placebo in adolescents with Mania in Bipolar I Disorder. The primary efficacy measure was the change from baseline to Endpoint of the Adolescent Structured Young-Mania Rating Scale (YMRS) total score.

In Study HGIN, 99 subjects were planned in a 2:1 ratio to have 80% power at the Type I error rate of 0.05 to test a treatment group difference of 7.93, a common standard deviation estimate of 12.15. One hundred and fifteen subjects entered the study. Of these, 107 (72 to olanzapine and 35 to placebo) were randomized and 64 subjects (49 to olanzapine and 15 to placebo) completed the acute phase of the study. Seventy two percent (72%) of the patients were Caucasian and 22% were Africa-Americans. Seventy percent (70%) were male and 30% were female. All the patients were between 13 and 17 years of age (inclusive).

In Study HGIU, 130 to 200 subjects were planned in a 2:1 ratio to have 80% power at the Type I error rate of 0.05 to detect an anticipated treatment group difference of 7.00, a common standard deviation estimate of 12.50. Two hundred and three subjects entered the study. Of these, 161 (107 to olanzapine and 54 to placebo) were randomized and 120 subjects (85 in olanzapine and 35 in placebo) completed the acute phase of the study. Seventy percent (70%) of the patients were Caucasian, 16% Hispanics and 9% were Africa-Americans. More than half were male. All the patients were between 13 and 17 years of age (inclusive).

After the screening and washout period (2 days to 2 weeks for screening and washout), subjects in Study HGIN were treated for 6 weeks, and subjects in Study HGIU were treated for 3 weeks, during a double-blind phase.

1.3 Statistical Issues and Findings

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies. In Study HGIN, the primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. In Study HGIU, the primary efficacy measure was the change from baseline to Endpoint of the YMRS total score. The treatment efficacy was analyzed using ANCOVA with LOCF data.

In Study HGIU, the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder is supported by both the primary efficacy results using LOCF, and the results using OC and MMRM. In Study HGIN, however, the efficacy results using OC and MMRM strongly contradict that of the LOCF result. Both the OC and MMRM results are highly nonsignificant. Although LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. This is not the case in this study. On the other hand, MMRM yields quite reliable result if patient dropout mechanism depends only on the observed data, not on unobserved ones. This seems to be a more reasonable assumption. Indeed, the individual outcome profile plots indicate that most dropouts happened when there were no obvious improvements. On the other hand, both the population mean profile plot and individual profile plot suggest that the difference between treatment groups only occurred in the patients who dropped out before the Endpoint. Together, Study HGIN does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents (ages 13 to 17) with schizophrenia.

2. INTRODUCTION

2.1 Overview

In this submission, two efficacy studies were submitted for the evaluation of the efficacy and safety of olanzapine in doses from 2.5 to 20 mg/day in the treatment of adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU) (Table 2.1). In the pooled pivotal Studies HGIN and HGIU, a total of 268 subjects were randomized. Of those, 179 subjects were in the olanzapine group (2.5 to 20mg/day) and 89 subjects were in the placebo group. The numbers of subjects in these studies are given in Table 2.1.

Table 2.1: Studies Supporting the Efficacy of Olanzapine

Protocol	Study Description	Study Treatment	No. of Subjects ^a
Study HGIN	6-week, randomized, double-blind, placebo-controlled, multicenter, flexible dose study	Placebo	35
		Olanzapine (flexible doses)	72
Study HGIU	3-week, randomized, double-blind, placebo-controlled, multicenter, flexible dose study	Placebo	54
		Olanzapine (flexible dose)	107

a: Includes all subjects who were randomized.
Source: FDA analysis.

2.2 Data Sources

The Clinical Study Reports and SAS transport data sets for the studies were provided in electronic form in \\CDSESUB1\N20592\S_040\2006-10-30.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Efficacy studies were designed to evaluate the efficacy and safety of olanzapine compared with placebo in adolescents (ages 13 to 17) with Schizophrenia (Study HGIN) and adolescents with Mania in Bipolar I Disorder (Study HGIU). In both studies, eligible subjects were randomly assigned to receive olanzapine or placebo in a 2:1 ratio (Table 2.1). The subjects received a screening or washout period of 2 to 14 days before randomization. Following randomization, all subjects went through a 6-week (3-week for Study HGIU) double-blind acute period starting with 2.5 or 5mg/day of olanzapine or placebo given once daily. The dose was increased by 2.5 or 5 mg/day dose increments at the investigator’s discretion to the maximum tolerable dose, not to exceed 20 mg/day.

In Study HGIN, the primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. The secondary measures included CGI-I, CGI-S, PANSS total score and Overt Aggressive Scale (OAS), ECGs, AIMS, CHQ and BACS. In Study HGIU, the primary efficacy measure was the change from baseline to Endpoint of the Y-MRS total score. The secondary measures included Y-MRS individual scores, CGI scale Bipolar Version Severity of Illness, CDRS-R, OAS, EPS, AIMS, CHQ and CGI-S.

Eligible subjects were from 13 to 17 years of age. Patient must have a diagnosis of schizophrenia according to DSM-IV-TR and confirmed by the K-SADS-PL in Study HGIN. Patients were diagnosed as bipolar I disorder and currently displayed an acute manic or mixed episode according to DSM-IV-TR in Study HGIU.

3.1.1 Baseline Demographic Characteristics

The patient baseline demographic characteristics are summarized in Tables 3.1 to 3.2 for these two studies. In Study HGIN, the majority of patients were male, Caucasian, and from the United States. The mean age of patients in the study was 16.1 years in the olanzapine treatment group and 16.3 years in the placebo group. There were 71% males and 29% females in the olanzapine group, 69% males and 31% females in the placebo group. In Study HGIU, the majority of patients were Caucasian and from the United States, with a mean age of 15.1 years in the olanzapine group and 15.4 years in the placebo group. There were 57% males and 43% females in the olanzapine group, 44% males and 56% females in the placebo group. Patient demographic characteristics were not significantly different between treatment groups at baseline.

Table 3.1 Demographic Characteristics for Study HGIN at Baseline of Period II

Demographic Variables	Statistics/Category	Therapy		*P-value
		Olanzapine	Placebo	
		(N=72)	(N=35)	
		n (%)	n (%)	
Gender	Male	51 (70.83)	24 (68.57)	.825
	Female	21 (29.17)	11 (31.43)	
Age	No. of Patients	72	35	.536
	Mean	16.14	16.30	
	Median	16.31	17.00	
	Std. Dev.	1.25	1.55	
	Minimum	13.03	13.06	
Origin	Maximum	17.99	18.00	.656
	African Descent	17 (23.61)	7 (20.00)	
	Caucasian	52 (72.22)	25 (71.43)	
	Hispanic	2 (2.78)	1 (2.86)	
Country	Other	1 (1.39)	2 (5.71)	1.00
	America	38 (52.78)	19 (54.29)	
	Russia	34 (47.22)	16 (45.71)	

* Frequencies are analyzed using the Fisher's Exact Test

Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA); Model= Country Therapy

Source: Table HGIN.11.1 of sponsor's HGIN Study Report.

Table 3.2 Demographic Characteristics for Study HGIU at Baseline Period II

Demographic Variables	Statistics/ Category	Olanzapine	Placebo	*P-value
		(N=107)	(N=54)	
		n (%)	n (%)	
Gender	Male	61(57.01)	24(44.44)	.137
	Female	46(42.99)	30(55.56)	
Age	No. of Patients	107	54	.250
	Mean	15.14	15.38	
	Median	15.12	15.41	
	Std. Dev.	1.28	1.20	
	Minimum	13.02	13.07	
Origin	Maximum	17.89	17.68	.247
	African Descent	13(12.15)	2(3.70)	
	Caucasian	71(66.36)	41(75.93)	
	East/Southeast Asian	0(0.0)	1(1.85)	
	Hispanic	18(16.82)	8(14.81)	
Country	Other	5(4.67)	2(3.70)	1.00
	America	95(88.79)	48(88.89)	
	Puerto Rico	12(11.21)	6(11.11)	

* Frequencies are analyzed using a Fisher's Exact Test

Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA); Model= Country Therapy

Source: Table HGIU.11.1 of sponsor's HGIN Study Report.

3.1.2 Baseline Disease Characteristics

Across the individual studies, the baseline disease characteristics between the treatment and placebo groups were compared.

In Study HGIN, there were no statistically significant differences between the two treatment groups on the age of onset, the number of previous schizophrenia episode, the total cumulative hospitalization in months, the length of current episode in days, the BPRS-C total score and corresponding subtotal scores.

In Study HGIU, The treatment groups differed considerably at baseline on several illness characteristics. Patients in the placebo group had greater numbers of previous manic, depressive, and mixed episodes. Patients in the olanzapine treatment group had much higher baseline scores on the CGI Severity of Depression scale. In addition, the treatment groups differed on several subscales of the CHQ at baseline. Finally, considerably more patients in the olanzapine treatment group reported a paternal history of psychosis and a history of psychiatric hospitalization at baseline. These are depicted in Table 3.3. The different Quality-of-Life scores at baseline in CHQ are given by the sponsor in Table HGIU.11.9 in the Clinical Study Report. A more specific assessment of these differences will be made by the medical officer.

Table 3.3 Patient Differences in Illness Characteristics and Family History at Baseline in Study HGIU

Illness Characteristics	Placebo	Olanzapine	P-value
No. Prev. Mania Episode	(N=54) 4.43 (8.95)*	(N=106) 2.07 (4.97)	0.048
No. Prev. Depression Episodes	(N=46) 3.98 (8.26)	(N=92) 1.60 (2.84)	0.014
No. of Prev. Mixed Episodes	(N=50) 3.85 (9.40)	(N=92) 1.19 (3.65)	0.027
CGI Severity Depression	(N=46) 2.65 (1.60)	(N=81) 3.14 (1.57)	0.043
Paternal History of Psychosis- Father	N=54 0/51/3† (N=54)	(N=107) 8/78/20 (N=106)	0.025
Paternal History of Hospitalization	9/45‡ (N=54)	34/72 (N=106)	0.040

*Standard Deviation. †Yes/No/Unknown. ‡Yes/No.

Source: Tables HGIU.11.2, HGIU.11.6 in Clinical Study Report.

3.1.3 Patient Discontinuation

In Study HGIN, 107 subjects were randomized and 63 (60%) subjects completed the 3-week double-blind phase of the study (Table 3.4), including 49 (32%) subjects from the olanzapine group and 15 (43%) from the placebo group. Lack of efficacy was the most common reason for early termination in both groups. But there was a dramatic difference, which was also statistically significant in nominal sense, between the two treatment groups. In the placebo group, eighteen (51%) patients dropped because of lack of efficacy and the corresponding number for the olanzapine group was 10 (14%).

In Study HGIU, 161 subjects were randomized and 120 (74.5%) completed the 3-week double-blind phase, as shown in Table 3.4. The most common reason for the early withdrawal in both treatment groups was the Lack of Efficacy which had a total of 28 subjects (17.4%). Sixteen (30%) patients dropped out of study because of lack of efficacy in the placebo group and the corresponding number in the olanzapine group was 12 (12%). The difference between the two treatment groups is highly statistically significant in nominal sense (p-value = 0.007).

Table 3.4 Number (%) of Subjects Who Discontinued Treatment During the Double-Blind Period by Primary Reason for Withdrawal in Studies HGIN and HGIU

	Placebo	Olanzapine	Overall
Study HGIN	(N=35)	(N=72)	(N=107)
Total withdrawal	20 (57.1%)	23 (31.9%)	43 (40.2%)
Reason for Withdrawal			
Adverse event	0	5 (6.9)	5 (4.7)
Lack of efficacy	18 (51.4)	10 (13.9)	28 (26.2)
Patient decision/ Personal conflict	1 (2.9)	4 (5.6)	5 (4.7)
Noncompliance	1 (2.9)	2 (2.8)	3 (2.8)
Sponsor decision	0	1 (1.4)	1 (0.9)
Lost to follow-up	0	1 (1.4)	1 (0.9)
Study HGIU	(N=54)	(N=107)	(N=161)
Total withdrawal	19 (35.2%)	22 (20.1%)	41 (25.5%)
Reason for Withdrawal			
Adverse event	1 (1.9)	3 (2.8)	4 (2.5)
Lack of efficacy	16 (29.6)	12 (11.2)	28 (17.4)
Patient decision/Personal conflict	1 (1.9)	4 (3.7)	5 (3.1)
Non-compliance	1 (1.9)	0	1 (0.6)
Physician decision	0	1 (0.9)	1 (0.6)
Other	0	2 (1.9)	2 (1.2)

Source: Tables HGIN.10.1 and HGIU.10.1 – Results in Clinical Study Report.

3.1.4 Statistical Issues and Results

According to the protocol, efficacy analyses were performed on an intent-to-treat (ITT) basis. An ITT analysis defines the treatment groups as those to which patients were assigned by random allocation, even if a patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. For each efficacy variable, the analysis included all randomized patients with baseline and post baseline observations. Using LOCF for missing observations, only patients with a baseline and a post baseline measure were to be included in the analysis. 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.

According to the protocol, the null hypothesis for primary analysis was that there was no difference between treatment groups in the mean change from baseline to Endpoint in the BPRS-C total score for Study HGIN (the YMRS total score for Study HGIU). For efficacy analyses, baseline was defined as the

last observation prior to the end of Study Period II of the study (the period for efficacy study) and Endpoint was defined as the last observation within the period. This was analyzed using the ANCOVA model which included baseline score as covariate, treatment and country as factors.

Interim Analyses: According to the protocol, an interim analysis might be conducted after approximately half of the required patients finished the double-blind acute therapy phase of the study, regardless of whether they completed the 6-week double-blind therapy or discontinued from the double-blind therapy. This interim analysis was planned with the intent to terminate the double-blind phase if overwhelming efficacy of olanzapine was shown. If enrollment was faster than initially anticipated, the sponsor might elect not to conduct the interim analysis. Statistical evidence of overwhelming efficacy was defined to be a statistically significant difference between the placebo and olanzapine group in the change from baseline to Endpoint of the BPRS-C total score, consistent with the primary efficacy analysis, at the $\alpha=0.0294$ level. In the final analysis, the treatment comparison on the BPRS-C total score would also be tested at $\alpha=0.0294$ level. This adjustment followed the methodology described in Pocock (1977).

STUDY HGIN

The protocol for this study was approved by the sponsor on 15 July 2002 and was amended on: 17 October 2002; 03 February 2004; and 08 July 2004. According to the sponsor, the statistical analysis plan (SAP), which supersedes the statistical plans described in the protocol, was approved on 10 June 2005, the same day the reporting database was validated and subsequently locked for analysis. The sponsor made substantial changes on Version C of the protocol. The SAP was not submitted to FDA for review until 21 March 2006, upon the request of the agency. Some changes were made to the planned analyses outlined in the Final SAP after the unblinding of the database. These additional analyses did not alter the interpretation of the primary efficacy analysis of this study (See 9.8.2.2.1 of the Clinical Study Report).

Based on the data set of Study HGIN, the normality test for the primary endpoint gives a p-value of 0.76 using the Shapiro-Wilk test, density plot also shows a symmetric and single mode distribution so the normality assumption is not seriously violated in my opinion. Therefore, no nonparametric method is used on the efficacy test. The analysis results are presented in Table 3.7.

According to the sponsor, the interim analysis was not conducted.

Using the data sets provided by the sponsor, the reviewer confirmed the efficacy results on LOCF data set. The ANCOVA with the primary efficacy measure gave similar significance results as reported in the Clinical Study Report. The homoscedasticity was assessed through the plot of residuals against the predicted values from ANCOVA model on the primary efficacy measure. No heteroscedasticity was found from the plots.

Given the high percentages of patient dropout as indicated in Table 3.4, the reliability and interpretability of the efficacy results becomes an issue. In general, LOCF procedure is reliable only when the mean outcome measure is stable over the whole study period. This is obviously not the case as the mean BPRS-C total score decreased 24.5 points from a baseline mean of 56 for those stayed to the Endpoint of Study Period II. Alternatively, the MMRM method gives reliable efficacy results if the patient dropouts were non-informative, with dropouts only depending on the observed outcome values, not on the unobserved values. This seems to be a reasonable assumption in this study.

Table 3.7: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Studies HGIN --- ITT Population

	Placebo	Olanzapine
Study HGIN	(N=35)	(N=72)
N (Analysis population)	35	72
N (BPRS-C Total Score)	35	72
Baseline Mean	50.1	50.3
Median change from baseline	-9.3	-19.4
ANCOVA Analysis (LOCF)		
LS Mean change from baseline (SE) ^a	-9.1 (2.73)	-19.3 (1.91)
Difference between LS Means and C.I. ^a	-10.1 (-16.7, -3.5)	
P-value ^a	0.003	
MMRM Analysis		
LS Mean change from baseline (SE) ^b	-23.5 (3.06)	-24.7 (1.70)
Difference between LS Means and C.I. ^b	-1.25 (-8.11, 5.61)	
P-value ^b	0.72	
OC Analysis		
N (BPRS-C Total Score)	15	50
LS Mean change from baseline (SE) ^c	-24.1 (3.35)	-24.4 (1.82)
Difference between LS Means and C.I. ^c	-0.25 (-7.9, 7.4)	
P-value ^b	0.95	

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.

b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

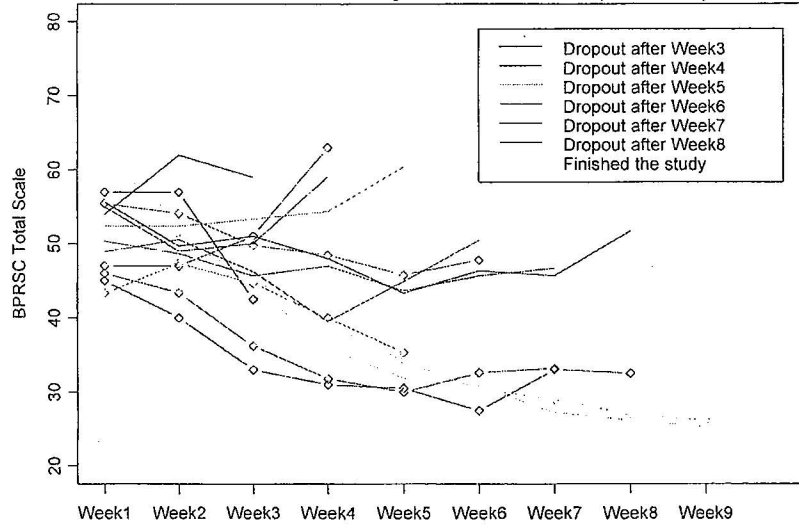
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.

Note: Negative change in score indicates improvement.

Source: Reviewer.

Using the data sets provided by the sponsor, the OC and MMRM analyses yield statistically **very non-significant** efficacy results for the primary outcomes. OC analysis yields a **p-value of 0.95** while MMRM analysis yields a **p-value of 0.72**. These results contradict that of the LOCF analysis on the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. To see why this is the case, this reviewer plotted both the population mean profiles and individual profiles for both treatment groups. These are depicted in Figures 3.1 to 3.3.

Figure 3.1: Population Mean Profiles by Dropout Time for BPRSC Total Scale by Treatment Group -- Study HGIN



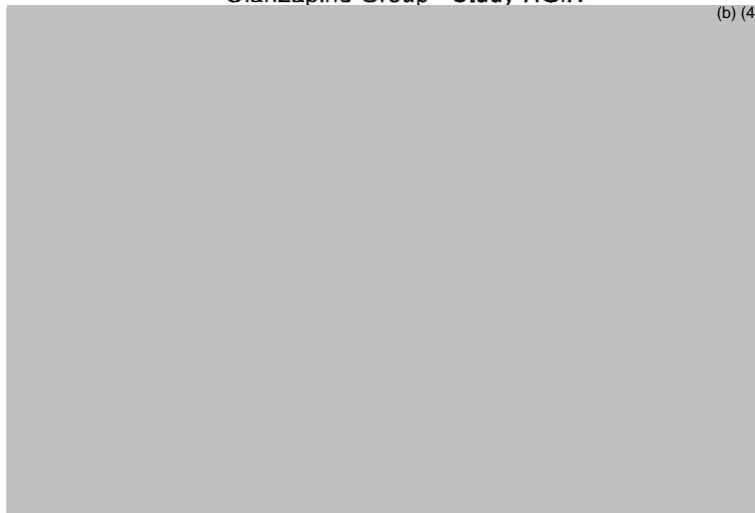
Source: Reviewer

Figure 3.2: Patient Profiles of BPRSC Total Score Placebo Group – Study HGIN



Source: Reviewer

Figure 3.3: Patient Profiles of BPRS-C Total Score
Olanzapine Group - Study HGIN



Source: Reviewer

These figures clearly indicate that there appears to be no difference between the treatment groups among those who stayed to the end of Period II of the study. The difference appears only among those who dropped out before the end of Period II. Among those patients, olanzapine seems to have improved patient BPRS-C total score over placebo. In fact, Figures 3.2 and 3.3 seem to indicate that olanzapine reduced the BPRS-C total score in both the dropout group and the non-dropouts group while placebo reduced the score only in the non-dropouts group, not in the dropouts group.

This phenomenon was observed in both US and Russia.

STUDY HGIU:

The protocol for this study was approved by the sponsor on 15 July 2002. According to the sponsor, the statistical analysis plan (SAP) addressed the planned statistical analyses prior to unblinding, and was approved prior to the unblinding of the reporting database. The sponsor stated that the SAP was approved on 21 June 2005. The reporting database was validated and subsequently locked for analysis on 24 June 2005. It was not submitted to the Agency for review until 26 March 2006.

Of the 161 randomized patients, 159 were analyzed for the primary efficacy measure. Two of the patients randomized to receive olanzapine did not have a post baseline observation that could be used for the primary efficacy analysis. In addition, the primary analysis, LOCF mean change from baseline to endpoint in the YMRS total score, was conducted without data from patients in Site 021. The efficacy result in Table 3.8 was derived using the data set provided by the sponsor with Site 021 included. Similar results were obtained when Site 021 was excluded.

Table 3.8: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Study HGIU --- ITT Population

	Placebo	Olanzapine
Study HGIU	(N=54)	(N=107)
N (Analysis population)	54	107
N (YMS-R Total Score) ITT	54	105
Baseline Mean	32.0	33.1
Median change from baseline	-6.5	-15.0
ANCOVA Analysis (LOCF)		
LS Mean change from baseline (SE) ^a	-10.0 (1.53)	-17.7 (1.27)
Difference between LS Means and C.I. ^a	-7.7 (-10.7, -4.6)	
P-value ^a	<0.0001	
MMRM Analysis		
LS Mean change from baseline (SE) ^b	-12.6 (1.28)	-17.8 (0.87)
Difference between LS Means and C.I. ^b	-5.6 (-8.7, -2.5)	
P-value ^b	0.0004	
OC Analysis		
N (BPRS-C Total Score)	37	88
LS Mean change from baseline (SE) ^c	-13.4 (1.70)	-19.1 (1.31)
Difference between LS Means and C.I. ^c	-5.7 (-9.2, -2.3)	
P-value ^b	0.0013	

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.

b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.

Note: Negative change in score indicates improvement.

Source: Reviewer.

Using the data sets provided by the sponsor, the reviewer confirmed the efficacy results in the Clinical Study Report. The efficacy result in the primary analysis was highly statistically significant. The OC and MMRM analyses were conducted by the reviewer and they yielded similar results as that of ANCOVA. These efficacy results are depicted in Table 3.8. These results all support the effectiveness of olanzapine in reducing the YMRS total score in adolescents with schizophrenia compared to placebo.

The treatment-by-country interaction for the primary efficacy measure was explored using the ANCOVA model, including baseline, country, treatment, and treatment-by-country interaction. The corresponding estimated treatment effect was -6.8, which was close to that in Table 3.8. But the p-value for treatment difference became 0.006. The interaction was not statistically significant. There were a total of 143 patients in US and 18 patients in Puerto Rico. In addition to including country as a factor in the efficacy model, statistical comparisons were made between treatment groups on the primary efficacy parameter in US alone and it yielded similar result.

In conclusion, the primary efficacy results using LOCF data set in both Studies HGIN and HGIU support the effectiveness of olanzapine in the treatment of schizophrenia in adolescent patients. However, only the

results in Study HGIU were supported by the results using OC data and MMRM procedure. The efficacy results using OC data set and MMRM strongly contradicted that using LOCF data set in Study HGIN. The OC and MMRM results were both highly nonsignificant. The population mean profiles and individual profiles suggest that the difference of the treatment effect only occurred among the patients who dropped out of the Period II of the study.

3.2 Evaluation of Safety

See medical review for detail.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Using LOCF data, subgroup analyses were performed on the primary efficacy measure, for age (younger than 15 years versus 15 years and older), gender and origin (Caucasian versus non-Caucasian) provided there were at least 10 patients in each treatment group. All subgroup analyses were considered exploratory. The treatment-by-subgroup interaction was tested using an ANCOVA model including the terms for baseline, treatment, country, subgroup, and the treatment-by-subgroup interaction. The treatment-by-subgroup interaction was tested to find out whether treatment differences in the mean primary efficacy measure were similar for each subgroup. In addition, the primary measure was analyzed for each country using the ANCOVA model including terms for baseline and treatment.

In both Studies HGIN and HGIU, neither sex nor the interaction between sex and treatment group was statistically significant at the nominal significance level of 0.05 in the ANCOVA analysis. The treatment effects and their significance levels stayed similar whether sex or the interaction between sex and treatment group was adjusted. However, Table 4.1 shows that the improvement on the primary endpoint was numerically larger for male than for female patients.

In both Studies HGIN and HGIU, neither age group (younger than 15 years versus 15 years and older) nor the interaction between age group and treatment was statistically significant at the nominal significance level of 0.05 in the ANCOVA analysis. The treatment effects and their significance levels were similar whether age group or the interaction between age group and treatment was adjusted. However, Table 4.2 shows that the improvement on the primary endpoint was numerically larger for older patients (15 years and older) than for younger ones.

**Table 4.1 Treatment Effect by Sex on the effect size in Studies HGIN and HGIU
(LOCF Analysis)**

Study	Placebo	Olanzapine
Study HGIN		
Male	N=24	N=51
Mean Change From Baseline of BPRS-C Total (SD)	-8.8 (17.5)	-19.7 (16.6)
Female	N=11	N=21
Mean Change From Baseline of BPRS-C Total (SD)	-10.5 (21.9)	-18.7 (12.8)
Study HGIU		
Male	24	60
Mean Change From Baseline of YMRS Total (SD)	-5.8 (9.35)	-16.8 (10.0)
Female	30	45
Mean Change From Baseline of YMRS Total (SD)	-9.3 (9.3)	-14.7 (10.1)

Source: FDA analysis.

**Table 4.2 Treatment Effect by Age Group on the effect size in Studies HGIN and HGIU
(LOCF Analysis)**

Study	Placebo	Olanzapine
Study HGIN		
Age below 15	N=7	N=15
Mean Change From Baseline of BPRS-C Total (SD)	-12.6 (20.4)	-17.3 (17.8)
Age 15 and Above	N=28	N=57
Mean Change From Baseline of BPRS-C Total (SD)	-8.5 (18.6)	-20.0 (15.0)
Study HGIU		
Age below 15	20	49
Mean Change From Baseline of YMRS Total (SD)	-9.5 (11.0)	-14.6 (10.2)
Age 15 and Above	34	56
Mean Change From Baseline of YMRS Total (SD)	-6.7 (8.4)	-17.0 (9.9)

Source: FDA analysis.

**Table 4.3 Treatment Effect by Country on the effect size in Study HGIN
(LOCF Analysis)**

Study	Placebo	Olanzapine
Study HGIN		
USA	N=19	N=38
Mean Change From Baseline of BPRS-C Total (SD)	-15.0 (18.3)	-21.2 (16.3)
Russia	N=16	N=34
Mean Change From Baseline of BPRS-C Total (SD)	-2.6 (17.4)	-17.4 (14.5)

Source: FDA analysis.

To explore the treatment effect in different countries, we noted that there were about 89% patients in US and only 11% patients in Puerto Rico in Study HGIU, so efficacy analysis was considered in US alone. In Study HGIN, country was not statistically significant at the nominal level of 0.05 but the interaction between country and treatment group yielded a p-value of 0.15 in the ANCOVA analysis. However, Table 4.3 suggests that treatment effect of olanzapine over placebo occurred mainly in Russian rather than in US patients. From Figure 4.1, it appears that the Russian patients in placebo group received very little improvement. Of the 16 patients in the placebo group, 10 dropout patients hardly received any

improvement by the time when they dropped out. The remaining 6 received very limited improvement. Of the 34 patients in the olanzapine group, only 8 dropped out. The improvement in this group appeared to be in line with that of the US patients.

Figure 4.1 Patient Profiles for BPRSC Total Score, by Country



Source: Reviewer.

4.2 Other Special/Subgroup Populations

Not available.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Studies HGIN and HGIU were 6-week (Study HGIU was 3-week), Phase IV, multicenter, randomized, double blind, placebo-controlled, flexible-dose studies with treatment arms of olanzapine and placebo for adolescent outpatients in the United States, Russia and Puerto Rico. The primary objective for Study

HGIN was to assess the efficacy and safety of olanzapine (2.5 to 20 mg/day) in the treatment of adolescents (ages 13 to 17) with schizophrenia. The primary efficacy measure was the change from baseline to Endpoint of the BPRS-C total score. In Study HGIU, the primary objective was to evaluate the efficacy and safety of olanzapine (2.5 to 20mg/day) in the treatment of adolescents with Mania in Bipolar I Disorder. The primary efficacy for the study was the YMRS total score. In both studies, the primary efficacy analyses were performed on the primary efficacy measure using the ANCOVA procedure with LOCF data.

In Study HGIU, the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder is supported by both the primary efficacy results using LOCF, and the sensitivity analysis results using OC and MMRM. In Study HGIN, however, the efficacy results using OC and MMRM strongly contradict that of the LOCF result. Both the OC and MMRM results are highly nonsignificant. Although LOCF yields highly significant efficacy result, this procedure is reliable only when efficacy measures are stable over the study period. This does not seem to be the case in this study. On the other hand, MMRM gives quite reliable result if patient dropout mechanism depends only on the observed data, not on unobserved ones. This seems to be a more reasonable assumption in this study. Indeed, the individual outcome profile plots suggest that most dropouts happened when there were no obvious improvements. On the other hand, both the population mean profile plot and individual profile plot suggest that the difference between treatment groups only occurred in the patients who dropped out before the Endpoint. Together, Study HGIN does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents (ages 13 to 17) with schizophrenia.

5.2 Conclusions and Recommendations

In this submission, the sponsor conducted 2 pivotal short-term olanzapine studies between November 2002 and May 2005 in the United States, Russia and Puerto Rico. The primary objective of Study HGIN was to evaluate the efficacy and safety of olanzapine in the treatment of the adolescents (ages 13 to 17) with schizophrenia. The primary objective of Study HGIU was to evaluate the efficacy and safety of olanzapine in the adolescents with Mania in Bipolar I Disorder. The primary efficacy measure for Study HGIN was the change from baseline to Endpoint of the BPRS-C total score and the primary efficacy measure for Study HGIU was the change from baseline to Endpoint of the YMRS total score.

In the two studies, only Study HGIU supports the effectiveness of olanzapine in the treatment of adolescent patients with Mania in Bipolar I Disorder. Study HGIN, however, does not provide enough support to the claim of the effectiveness of olanzapine in the treatment of adolescents with schizophrenia. Indeed, the difference between treatment groups only occurred in the patients who dropped out of Period II of the study.

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James Hung
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020592 / S-035, 039, 040, 041, 049,053, 055

021086 / S-21, 031, 032, 034

021253 / S-037, 039, 043

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

Clinical Pharmacology/Biopharmaceutics Review BPCA Summary Review

PRODUCT (Generic Name):	Olanzapine
PRODUCT (Brand Name):	Zyprexa
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	2.5, 5, 7.5, 10 and 20 mg
NDA:	20-592/040,041(SE5)
NDA TYPE:	Supplement for Schizophrenia and Bipolar disorder in adolescents in response to FDA Pediatric Written Request Letter
SUBMISSION DATE:	October 30, 2006
SPONSOR:	Eli Lilly
OND DIVISION:	HFD

EXECUTIVE SUMMARY

Olanzapine is currently indicated in the treatment of schizophrenia or bipolar I in adults. Previous studies in children and adolescents have shown a progressive increase in olanzapine concentrations with corresponding increases in dose. The data also suggested that pediatric patients generally have olanzapine plasma concentrations similar to those for adults for a given weight-adjusted dose. This sNDA provides information on the clearance of olanzapine in adolescents age 13-17 years with varying doses of 2.5 to 20 mg/day.

This sNDA includes a population pharmacokinetic study done in adolescents using flexible doses between 2.5mg/day to 20 mg/day.

The population pharmacokinetic study was done in 105 patients (Study F1D-MC-HGMF). Study duration was 4 and ½ weeks and the study population consisted of 64 males and 41 females.

The overall conclusions from the pharmacokinetic study in adolescents were:

- The exposure at steady-state in adolescents was 30-63% higher than in adults.
-
- Clearance in female adolescents was found to be 28% lower than in male adolescents.

RECOMMENDATION

From a Clinical Pharmacology/Biopharmaceutics perspective this sNDA is acceptable with the labeling changes suggested by the reviewer.

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**Office of Clinical Pharmacology and Biopharmaceutics/
Pharmacometrics Review**

NDA: 20-592-SE5/040, 041

Compound: Olanzapine
 Submission Dates: October 30, 2006
 Sponsor: Eli Lilly
 Reviewer: Andre Jackson

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Executive Summary

A study was done combining data from several centers in adolescents ages 13-17 to determine if the pharmacokinetics were similar or different from that previously observed in adults. The study data from 4 study sites were analyzed by mixed effects modeling to identify any important covariates which impacted Olanzapine pharmacokinetics in adolescents. The study results indicated that weight and gender were the significant covariates which influenced the clearance of Olanzapine in the subject population. Clearance/F in females was found to be 13.6 L/hr whereas that for males was 17.5 L/hr. Exposure in adolescents was higher due to their lower average body weights.

Introduction

Study F1D-MC-HGMF (Study HGMF) was performed to address the request by the United States (US) Food and Drug Administration (FDA) to provide pharmacokinetic information in a population of adolescent patients with schizophrenia or bipolar I disorder. Previous studies in children and adolescents have shown a progressive increase in olanzapine concentrations with corresponding increases in dose. The data also suggested that pediatric patients generally have olanzapine plasma concentrations similar to those for adults for a given weight-adjusted dose (Studies F1D-MC-HGCS, F1D-MCHGCC).

In this report, the pharmacokinetic data from Study HGMF was combined with other existing adolescent pharmacokinetic data (Studies F1D-MC-HGCS, F1D-MCHGCR, F1D-MC-HGGC, and F1D-SB-LOAY) to characterize olanzapine pharmacokinetics in adolescents and to address pharmacokinetic aspects of the FDA Pediatric Written Request for olanzapine.

Summary

The goal of this study was to collect data for Olanzapine in a pediatric population to determine if the levels were similar or different from those observed in adult schizophrenia or bipolar I disorder subjects. Previous studies in adults showed that the CL/F was 13.6 L/hr with smoking and gender being important covariates. In the current analysis the sponsor has used a 1 compartment model similar to that used in adults and analyzed the data obtained following a 4.5 week study in adolescents ages 13-17 following the administration of doses ranging from 2.5 to 20 mg/day. Body weight and gender were identified as important covariates. The label claim from this analysis was

(b) (4)
However this was not accepted by OCP since the result was not consistent with the experimental data.

COMMENTS TO MEDICAL REVIEWER

OCP has revised the following portion of the label based upon the completed Pediatric Written Request:

The firm (b) (4)

This statement was deleted.

The firm also wanted to include a statement (b) (4)

However due to the poor quality of the prediction of the true steady-state values with the model, only the observed range of steady-state values was used.

OCP REVISED LABEL

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents had a lower average body weight compared to adults, resulting in an average range of olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients.

Objective of the analysis

The primary objective of this study was to characterize olanzapine pharmacokinetics (CL/F and V/F); the inter- and intra-subject variabilities of olanzapine pharmacokinetics; and the potential influence of patient factors such as age, weight, gender, ethnic origin, and smoking status on olanzapine pharmacokinetics in adolescents 13 to 17 years of age that have been diagnosed with schizophrenia or bipolar I disorder.

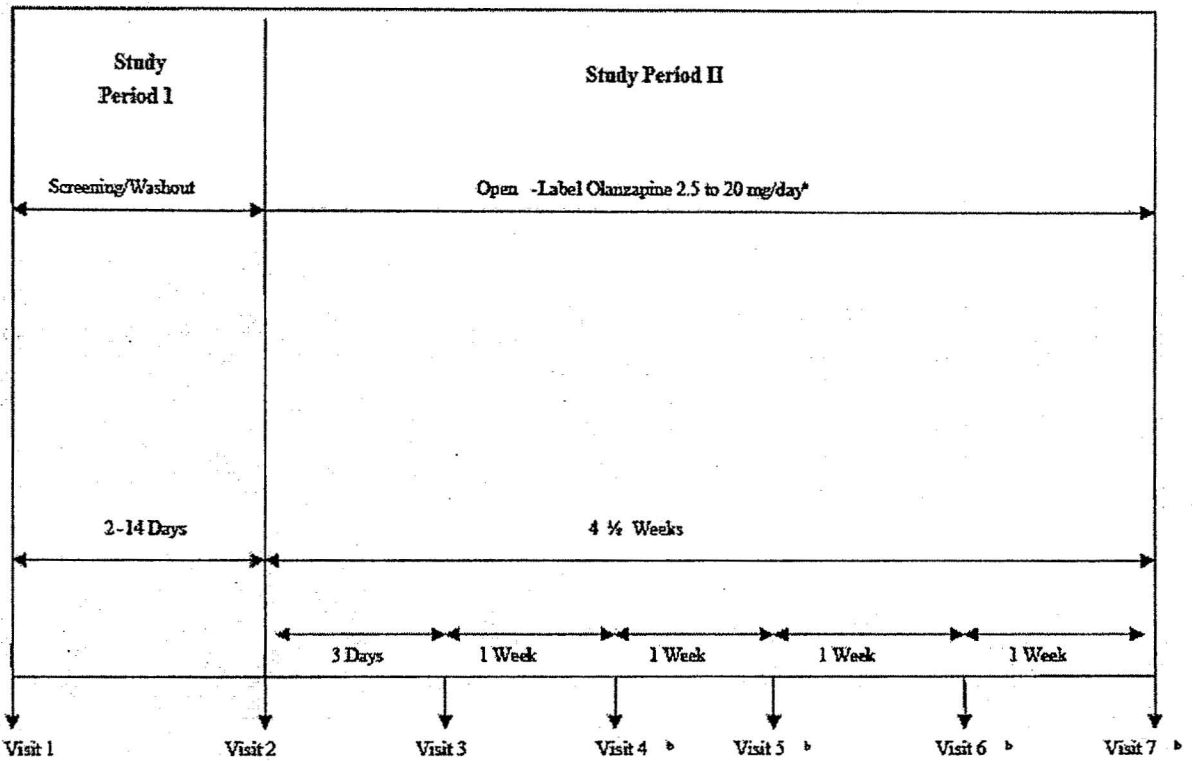
Methods

Design

Study#1:

Study HGMF was a multicenter, openlabel, single arm trial in adolescent patients (13 to 17 years) meeting diagnostic criteria for schizophrenia or bipolar I disorder as defined by the DSM-IV-TR . The study design consisted of two study periods:

Study Period I was a 2- to 14-day Screening and Washout Period, and Study Period II was a 4 and ½ -week Open-Label Treatment Period. In order to protect patient well-being, this study employed as short a washout period as practical and was consistent with washout periods typical of real-world clinical practice. Since the elimination half-life of most orally administered antipsychotics ranges from 20 to 40 hours and the half-life of decanoate depot preparations (for example, fluphenazine) ranges from 7 to 10 days , the washout period was appropriate for this patient population. Patients already taking olanzapine continued on their previous dosage (between 2.5 to 20 mg/day) unless a dose adjustment was deemed necessary by the investigator, while patients new to olanzapine therapy started on an initial dose of 2.5 to 5.0 mg/day, as determined by the investigator.



*The starting dose for olanzapine-naïve patients was 2.5 to 5 mg/day. For patients entering the study already on olanzapine treatment, the maximum initial dose was 20 mg/day.

^bPK sampling at Visits 4, 5, 6, and 7.

Table 1. Summary of Olanzapine Studies Included in the Adolescent Population Pharmacokinetic Evaluation

Study	Patient Population	Dose (mg) ^a	Sample Collection ^b	Patients and Observations
HGMF	• 80-100 adolescents • 13-17 years old • Diagnosed with schizophrenia or bipolar I disorder	• 2.5 - 20	• 4 blood samples per patient	• To be determined after database lock
LOAY	• 88 adolescents and young adults • 12-20 years old • Diagnosed with schizophrenia, shizoaffective or schizophreniform disorders	• 5 - 20	• 1 to 8 blood samples per patient	• 80 adolescents • 293 observations
HGCR/S	• 9 children and adolescents • 10-18 years old • Diagnosed with schizophrenia	• 2.5 - 20	• 9 to 15 blood samples per patient	• 6 adolescents • 84 observations
HGGC	• 23 children and adolescents • 5-14 years old • Diagnosed with bipolar disorder	• 2.5 - 20	• 1 to 4 blood samples per patient	• 5 adolescents • 15 observations

^aOlanzapine was administered as a once-daily (QD) oral dose

^bAll samples were collected at steady-state. Steady-state is defined as a patient being on a fixed olanzapine dose for at least 5 consecutive days.

Analytical

Assay Validation - Zyprexa

Parameter	Zyprexa
Method	Olanzapine was assayed by liquid chromatography with electrochemical detection (LCEC), using extracts based on its acid-base behavior.
Extract Stability	6 days
Number of Freeze-thaw	2 Cycles QC's 80, 40, and 0.64 ng/ml Diff=0.1%, -0.4% and --2.8%

Benchtop Stability at RT	4 hrs
Long term at -20° C -60C -80C	378 days 1017 days 8.5 months
Extraction Recovery	(b) (4) ng/ml ng/ml ng/ml Internal standard (b) (4) %

All samples stored at -80C

1.F1D-MC-HGGC

Date of first sample analysis: 13 April 1999

Date of last sample analysis: 20 April 1999

Date for 1st sample draw 2/27/98

Total storage time= 425 days

Table 2 Back Calculated Calibration Standard Concentration Data for HPLC Assay for Olanzapine in Human Plasma

Summary Statistics:

	Concentration (ng/mL)								
Nominal	100	50.0	25.0	10.0	5.00	2.50	1.00	0.500	0.250
Average	99.7	50.8	24.8	9.87	4.81	2.44	1.02	0.521	0.252
% Error	-0.3	1.7	-0.9	-1.3	-3.8	-2.5	2.1	4.2	0.8
N	2	2	2	2	2	2	2	2	2

Individual Results:

Batch	
S031	(b) (4)
S041	

Table 3 Control Results from the HPLC Assay for Olanzapine in Human Plasma

Summary Statistics:

	Concentration (ng/mL)			
Nominal	80.0	40.0	0.540	80.0 (DFAC of 6.67)
Average	84.9	42.9	0.703	82.4
Std. Dev.	1.80	1.17	0.0343	
Precision (%)			(b) (4)	
% Error	6.2	7.3	9.9	
N	4	4	4	2

Individual Results:

2.FID-MC-HGCS

Date of First Sample Analysis: 18/11/96 (d/m/y)

Date of Last Sample Analysis: 23/04/97 (d/m/y)

Date for 1st sample draw 10/25/95

Total storage time= 545 days

Table 2 Back-Calculated Calibration Standard Concentrations

	nominal olanzapine concentration (ng/mL)									
batch	100	50.0	25.0	10.0	5.00	2.50	1.00	0.500	0.250	
O00F	98.7	49.8	26.6	9.97	4.95	2.52	0.984	0.544	0.222	
O01F	99.8	50.2	24.4	9.64	6.13	2.39	1.00	0.436	note 1	
O02F	101	51.8	23.8	8.24	4.83	2.65	0.995	0.533	0.272	
O03F	99.3	50.3	25.5	9.92	4.96	2.52	1.01	note 2	0.244	
O04F	100	50.2	24.8	9.82	4.99	2.33	1.02	0.489	0.273	
n	5	5	5	5	5	5	5	4	4	
mean	99.9	50.5	25.0	9.52	5.17	2.48	1.00	0.500	0.253	
std dev	0.943	0.793	1.08	0.724	0.538	0.126	0.0140	0.0491	0.0245	
%rsd	0.9%	1.6%	4.3%	7.6%	10.4%	5.1%	1.4%	9.8%	9.7%	
% error	-0.1%	0.9%	0.0%	-4.8%	3.4%	-0.7%	0.3%	0.1%	1.1%	

Table 4 Assay Accuracy Data - QC Samples

batch	nominal Olanzapine concentration (ng/mL)					
	80.0	80.0	40.0	40.0	0.640	0.640
O00F	(b) (4)					
O01F	(b) (4)					
O02F	(b) (4)					
O03F	(b) (4)					
O04f	(b) (4)					
n	10		10		9	
mean	82.7		39.9		0.638	
std dev	2.53		1.92		0.0971	
% rsd	3.1%		4.8%		15.2%	
% error	3.3%		-0.2%		-0.3%	

3.F1D-MC-HGMF

Date for 1st sample draw 6/1/05

Total storage time=

Analytical Performance: Back-Calculated Concentrations (ng/mL) of LY170053 Calibration Standard in (Human) (Plasma - hep) in (Protocol 0062-05167)

Assay Date	Analytical Run Number	STD 0.250 ng/mL	STD 0.500 ng/mL	STD 1.00 ng/mL	STD 2.50 ng/mL	STD 5.00 ng/mL	STD 10.0 ng/mL	STD 25.0 ng/mL	STD 50.0 ng/mL	STD 100 ng/mL
11-Jan-2006	1	0.26	0.539	1	2.37	5.02	10.2	23.6	51.4	98.2
		0.244	0.507	0.997	2.44	5.02	9.74	24.6	51.2	101
12-Jan-2006	2	0.251	0.523	1.11	2.43	5.15	9.65	24	50.1	101
		0.269	*0.363	0.954	2.27	4.86	10	24.6	49.9	101
26-Jan-2006	4	0.256	0.477	0.874	2.24	4.77	9.72	22.9	48.3	97.4
		0.285	0.571	1.05	2.44	5.27	10.2	25.2	52.1	104
07-Mar-2006	5	0.262	0.557	1.02	2.41	4.96	9.55	23.3	49.7	102
		*0.347	0.528	*1.21	2.36	4.92	10.1	23.3	51	101
15-Mar-2006	6	0.244	0.488	0.98	2.4	5.05	9.82	24.3	50.8	100
		*0.165	0.473	1.01	2.76	4.95	10.7	25.4	51.1	97.7
22-Mar-2006	7	0.268	0.518	1.02	2.4	4.97	9.75	23.4	50.3	100
		0.213	0.535	0.995	2.47	5.52	9.99	24.2	51.1	101
27-Mar-2006	8	0.254	0.543	1.01	2.35	4.93	9.6	25.1	49.1	95.9
		0.22	0.545	1.07	2.38	5.17	9.23	25.2	55.1	101
Mean		0.252	0.523	1.01	2.41	5.04	9.88	24.2	50.8	100
S.D.		0.0202	0.0301	0.0565	0.119	0.189	0.36	0.829	1.59	2.11
%CV		8	5.8	5.6	4.9	3.8	3.6	3.4	3.1	2.1
%Bias		0.8	4.6	1	-3.6	0.8	-1.2	-3.2	1.6	0
n		12	13	13	14	14	14	14	14	14

Reason Deactivated

* F Calibration standard deactivated due to unacceptable % deviation

Analytical Performance of LY170053 Quality Control Samples in Human Plasma - hep (Protocol 0062-05167)

Run Date	Curve Number	QC 0.640 0.640 ng/mL	QC 40.0 40.0 ng/mL	QC 80.0 80.0 ng/mL	QC 180 180 ng/mL
11-Jan-2006	1	0.652	38.2	77.6	188
		0.663	39.6	76	183
12-Jan-2006	2	0.678	37.9	79.2	
		0.483	38.5	78.1	
26-Jan-2006	4	0.598	36.6	75.9	176
		0.693	41.4	79.9	195
07-Mar-2006	5	0.748	38.4	75.9	189
		0.707	37.3	75.5	276
15-Mar-2006	6	0.618	37.6	77.2	178
		0.566	39.2	77.2	166
22-Mar-2006	7	0.691	40.3	78.1	173
		0.672	43.8	76.2	176
27-Mar-2006	8	0.678	38.5	73.7	169
		0.664	42.1	70.2	176
Mean		0.651	39.2	76.5	187
S.D.		0.0665	2.02	2.41	29.2
%CV		10.2	5.2	3.2	15.6
%Theoretical		101.7	98	95.6	103.9
%Bias		1.7	-2	-4.4	3.9
n		14	14	14	12
Overall %CV		8.6			

Data:

Studies:

Pharmacokinetics

No dosing or sampling times were recorded during study LOAY. Each of the ten LOAY study sites provided a window of approximate sampling and dosing times. The firm did an analysis including and excluding the LOAY study however the FDA analysis only verified the analysis without the LOAY data set.

The times from dose for the concentrations were unknown because both actual time of last dose and the actual time of the blood sample were not collected in Study LOAY. Smoking status and ethnic origin information were not documented in Study LOAY.

Smoking status in Study HGMF was determined from the results of the cotinine test. Any concentrations reported as below quantification limit (BQL) were treated as missing values for the analyses.

Pharmacodynamics

N/A.

Data Checking

The data was checked by: perusing entered data to see if it was correct for units and definitions were consistent with entries. Data entry was consistent with the control stream. Scatter plots of the raw data were investigated to determine if the data contained a lot of outliers.

Models

Pharmacokinetics

Structural Model

Base Model Development

Pharmacokinetics of oral olanzapine in an adult population has been previously

characterized by a one compartment model (original NDA submission NDA (b) (4)). Therefore, a one compartment pharmacokinetic model with parameters such as absorption rate constant (K_a), oral clearance (CL/F), and oral volume of distribution (V/F) was initially tested to evaluate the adolescent pharmacokinetic data. The available data in adolescent patients did not allow reliable estimation of K_a , therefore, K_a was fixed to the adult population value. The base model was able to determine the inter-patient variability in CL/F and V/F with covariance using the omega block.

Three inter-patient variability models (Equation 1) were tested: η on CL/F , η on V/F and η on CL/F and V/F with covariance (omega block).

$$P = \Theta_1 \cdot \exp(\eta) \quad \text{Equation 1}$$

where P is the individual parameter estimate (CL/F or V/F), Θ_1 represents the typical or population value of the parameter and η is a random variable with a mean of zero and variance of ω^2 .

The difference between model predicted olanzapine plasma concentration and the observed olanzapine concentration was modeled using the residual error model. The two residual error models evaluated were proportional (Equation 2) and combined additive and proportional.

Parameter sensitivity analyses were performed on various base models and a final base model was selected for identification of potential significant covariates.

Final Model Development

All potentially significant covariates identified were added in combination to the base model to establish a full model. Each covariate was removed (one covariate at a time) from the full model. When the removal of a covariate from the full model resulted in a significant increase of the minimal objective function (≥ 10.828 , $p < .001$), that covariate was retained in the final model. In case of physiologically related, therefore highly correlated factors, such as age and weight, the covariate that best explained the data was selected for inclusion in the final model.

Covariate Models

Patient factors such as body weight, age, gender, ethnic origin, smoking status, and dose were tested for their influence on CL/F and V/F . Equations 3 to 5 were applied to test continuous covariates (body weight, age) and equation 6 to test categorical covariates (gender, ethnic origin, smoking status, and dose).

$$P = \theta_1 \cdot [1 + \theta_2 \cdot (\text{COV}-\text{MED})] \quad \text{Equation 3}$$

$$P = \theta_1 \cdot \text{EXP}[\theta_2 \cdot (\text{COV}-\text{MED})] \quad \text{Equation 4}$$

$$P = \theta_1 \cdot (\text{COV}/\text{MED})^{\theta_2} \quad \text{Equation 5}$$

$$P = \theta_1 \cdot (1 + \theta_2 \cdot \text{IND}) \quad \text{Equation 6}$$

where P is the individual parameter estimate, θ_1 represents the typical value of a parameter, θ_2 represents the effect of a covariate, COV is the value of a covariate, and MED is the median value of a covariate. IND is an indicator variable with a value of either 0 or 1 assigned for values of a categorical covariate (for example, smoker=0 and nonsmoker=1).

Each covariate was individually added to the base model and tested. When the objective function of the base model with a covariate was reduced by 6.635 ($p < 0.01$), the covariate was considered to be potentially significant.

Random Variance Models

Two residual error models evaluated were proportional (Equation 7) and combined additive and proportional.

$$C_{ij} = \text{IPRED} \cdot (1 + \text{ERR}) \quad \text{Equation 7}$$

where C_{ij} is the predicted j th olanzapine concentration in the i th patient, IPRED is the model predicted olanzapine concentration in the individual and ERR is a random variable with a mean of zero and variance of σ^2 .

Pharmacodynamics

N/A

Model Selection

Final Model Evaluation

Parameter sensitivity analysis and leverage analysis were applied to evaluate the robustness of the final model. Posterior predictive check was conducted to examine if the final model reliably predicts the data that was used to develop it.

Parameter Sensitivity Analysis

This analysis examined the parameter space, confirms the absence of local minima, and identifies the 95% confidence interval (CI) of the parameter using a process developed at Eli Lilly and Company (Allerheilgen et al. 1994, O'Brien et al. 1998). The analysis was

performed by fixing the parameter of interest to $\pm 5, 10, 15, 20, 30, 40\%$ of the population estimate and estimating all other parameters. The effect of modifying the parameter value on the overall fit of the data was examined. If needed, the parameter of interest was fixed to additional values up to $\pm 100\%$. The relationship between change in objective function and the parameter value was described using polynomial regression to obtain a 95% CI of the parameter. Assuming a chi-square distribution, the parameter values which produce a change in objective function of 3.841 represent the 95% confidence limits.

Leverage Analysis

The leverage analysis was performed to evaluate the contribution of subsets of patients on the final model. Ten datasets were created with 10% of the patients randomly omitted such that each patient was omitted only once. The final model was run with each dataset containing only 90% of the patients. The parameter estimates from all 10 runs were compared with the 95% confidence limits determined from the parameter sensitivity analysis.

Posterior Predictive Check

The final model parameter estimates, variance covariance matrix, and inter-patient variability estimates were used to perform simulations that predicted olanzapine concentrations at various olanzapine doses. The distributions of the predicted olanzapine concentrations were compared to the observed concentrations for each study.

Comparison of Adolescent and Adult Olanzapine Pharmacokinetics

Individual estimates of the pharmacokinetic parameters in adolescent patients were obtained from the final model post-hoc estimates. The pharmacokinetic model for oral olanzapine in adult patients from Study F1D-MC-HGAJ (original NDA 20-592, 21 September 1995) was developed in NONMEM, Version 4 using first order (FO) method of estimation. In an effort to be consistent with the software version and method of estimation used for adolescent pharmacokinetic modeling, the individual pharmacokinetic parameters in the adult patients were obtained by rerunning the final pharmacokinetic model for adult patients in NONMEM, Version V and using FOCE with interaction method.

Initial Model Selection

The basis of rejecting and/or accepting a particular model (e.g.: additive versus proportional, with or without weight, sex, etc.) should be described. The estimation method and the alpha level of the chi-square test should be included. Further, the type of model selection should also be presented (forward, backward, stepwise, etc.).

Final Model Selection

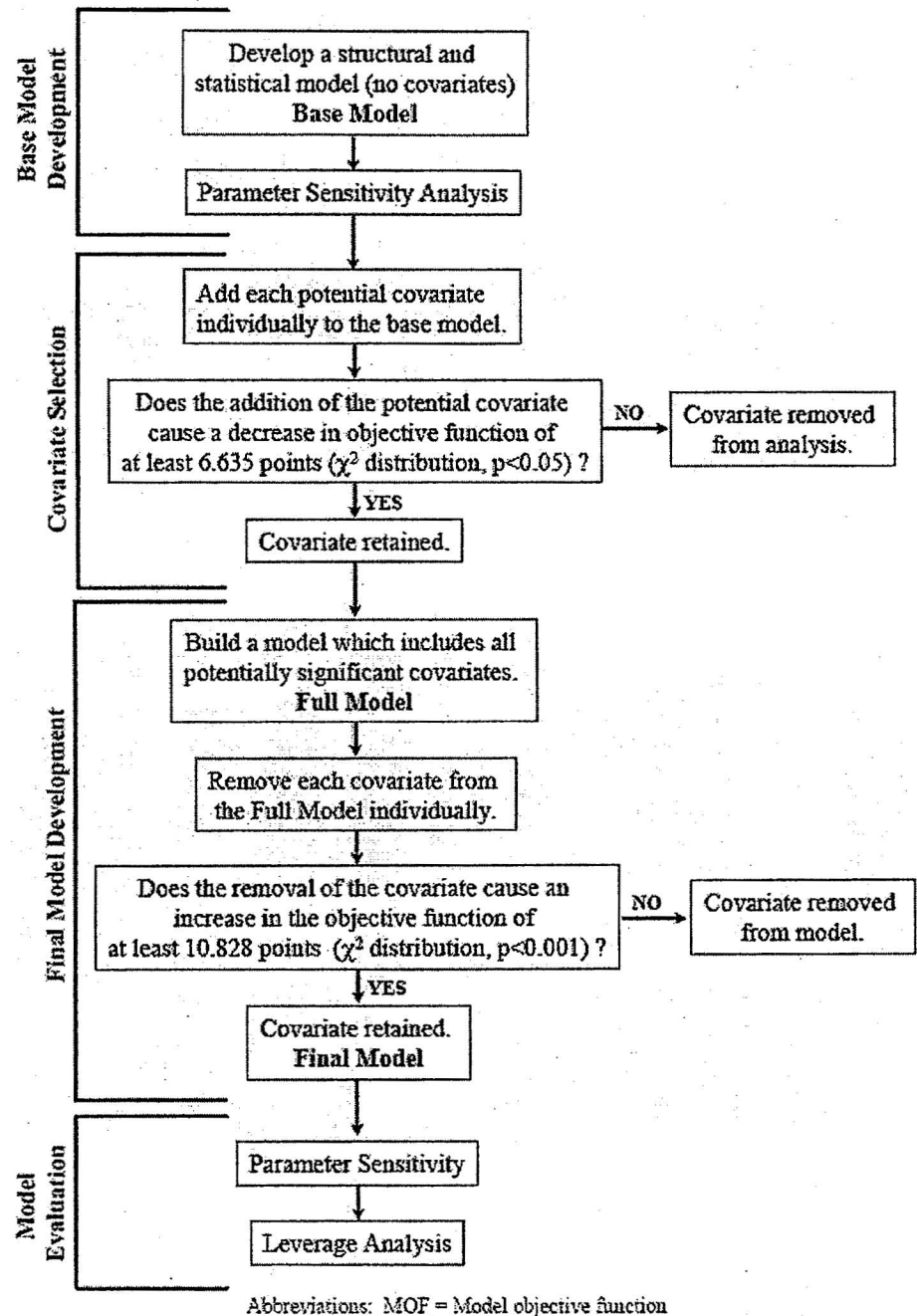


Figure HGMF.5.2. General process for pharmacokinetic model development

Software

The software used for the data formatting, modeling, simulation, graphing, and statistical tests should be included (e.g.; EXCEL, SAS, , S-PLUS, NONMEM version V,,).

Results and Discussion

Design Adequacy

Table HGMF.7.1. Baseline Demographics for Patients Included in the Pharmacokinetic Modeling (Studies HGCS, HGCR, HGCC, HGMF)

Demographic	HGCR	HGCS	HGCC	HGMF	Total
n	9	75	15	363	462
N	1	5	5	105	116
Age (years)					
Mean±SD	16	16.0±1.41	14.3±0.593	16.1±1.37	16.0±1.38
(Min, Max)		(14,17)	(13.3,14.7)	(13.43,17.99)	(13.3,17.99)
Body weight (kg)					
Mean±SD	78.9	65.6±15.8	65.3±10.4	72.9±20.9 ^a	72.3±20.3 ^b
(Min, Max)		(48.2,85.8)	(56.7,77.1)	(41.1,147.7) ^a	(41.1,147.7) ^b
Gender (N)					
Male	1	2	0	64	67
Female	0	3	5	41	49
Smoking status (N)					
Smoker	NA	NA	NA	20	20
Non-smoker	NA	NA	NA	73	73
Origin (N)					
Caucasian	NA	NA	4	90	94
African American	NA	NA	0	8	8
Hispanics	NA	NA	1	7	8

Abbreviations: n = number of observations; N = number of patients; Max = maximum; Min = minimum; SD = standard deviation; NA = not available.

^a n = 103

^b n = 114

The number of subjects appears adequate although it may have been better for them to have more subjects at age 13-14 to replace those in study LOAY.

Data Integrity

The data base contained subjects below 13 and above 17 who were excluded.

Model and Model Selection:

Base Model

Model description

Parameter estimation results

Table HGMF.7.3. Pharmacokinetic Parameters for the Base Population Model (Studies HGCS, HGCR, HGGC, HGMF)

	Units	Estimate	%SEE
Pharmacokinetic Model			
Absorption rate constant, K_a	hr ⁻¹	0.543 (Fixed)	-
Oral clearance, CL/F	L/hr	16.3	4.61
Oral Volume of Distribution, V/F	L	879	17.1
Interpatient Variability			
CL/F	%	45.9	15.9
V/F	%	68.8	42.3
Covariance between CL/F and V/F	-	0.258	22.5
Residual Error			
Proportional	%	27.0	13.7

Abbreviations: SEE = standard error of the estimate.

Goodness of fit

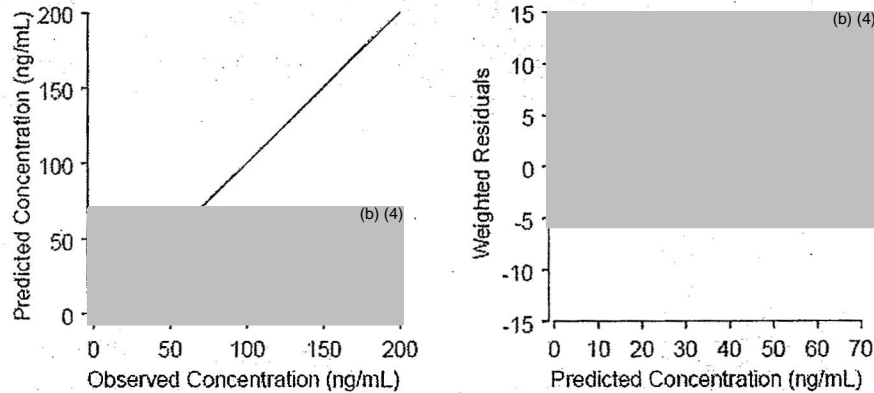


Figure HGMF.7.4. Goodness-of-fit plots for the base pharmacokinetic model. Data from Studies HGCS, HGCR, HGGC and HGMF.

Model Selection

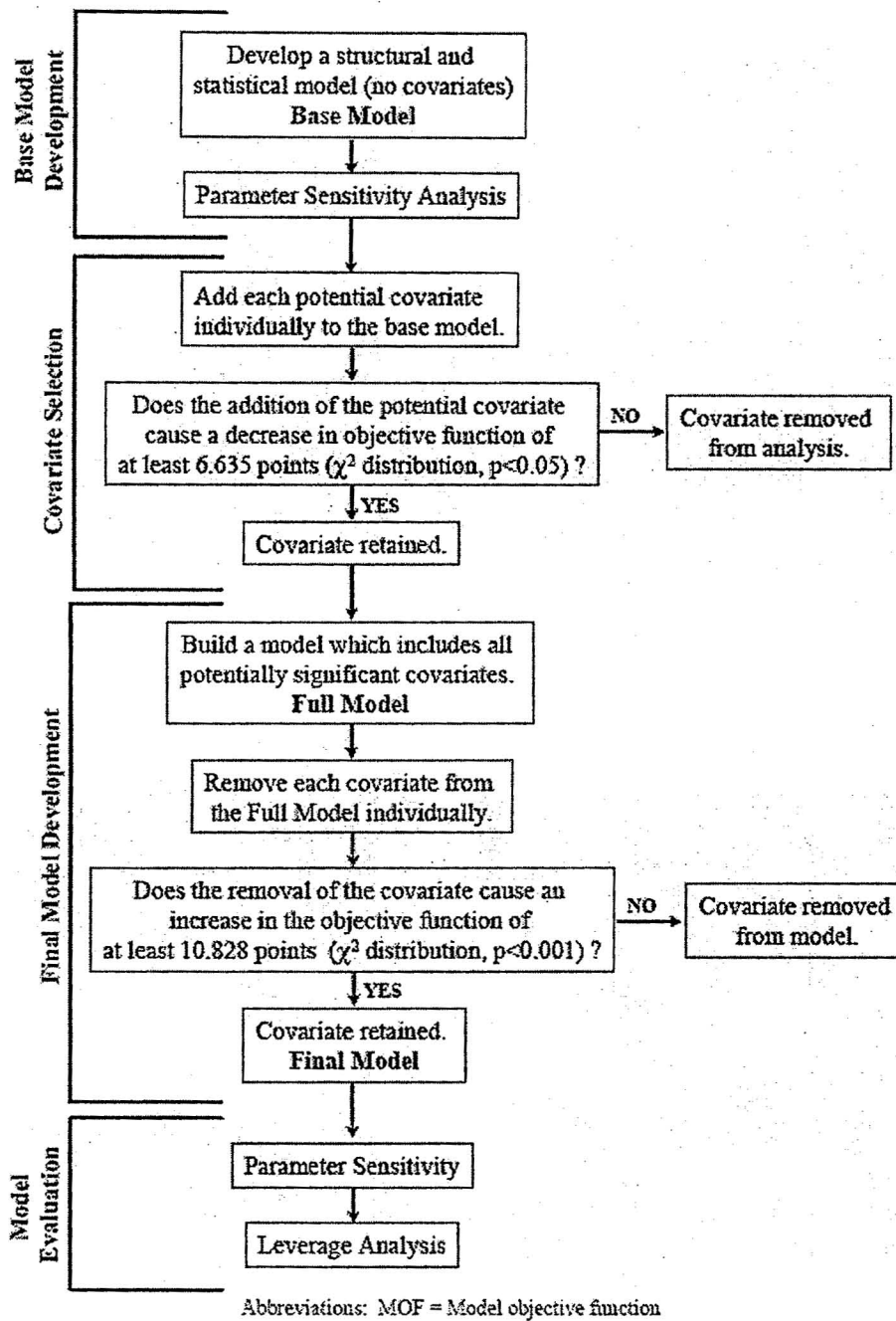


Figure HGMF.5.2. General process for pharmacokinetic model development

Final Model

Model description

Final Model Development

All potentially significant covariates identified were added in combination to the base model to establish a full model. Each covariate was removed (one covariate at a time) from the full model. When the removal of a covariate from the full model resulted in a significant increase of the minimal objective function (≥ 10.828 , $p < .001$), that covariate was retained in the final model. In case of physiologically related, therefore highly correlated factors, such as age and weight, the covariate that best explained the data was selected for inclusion in the final model.

Final Model Evaluation

Parameter sensitivity analysis and leverage analysis were applied to evaluate the robustness of the final model. Posterior predictive check was conducted to examine if the final model reliably predicts the data that was used to develop it.

Parameter Sensitivity Analysis

This analysis examines the parameter space, confirms the absence of local minima, and identifies the 95% confidence interval (CI) of the parameter using a process developed at Eli Lilly and Company (Allerheilgen et al. 1994, O'Brien et al. 1998). The analysis was performed by fixing the parameter of interest to ± 5 , 10, 15, 20, 30, 40% of the population estimate and estimating all other parameters. The effect of modifying the parameter value on the overall fit of the data was examined. If needed, the parameter of interest was fixed to additional values up to $\pm 100\%$. The relationship between change in objective function and the parameter value was described using polynomial regression to obtain a 95% CI of the parameter. Assuming a chi-square distribution, the parameter values which produce a change in objective function of 3.841 represent the 95% confidence limits.

Leverage Analysis

The leverage analysis was performed to evaluate the contribution of subsets of patients on the final model (Mandema et al. 1992). Ten datasets were created with 10% of the patients randomly omitted such that each patient was omitted only once. The final model was run with each dataset containing only 90% of the patients. The parameter estimates from all 10 runs were compared with the 95% confidence limits determined from the parameter sensitivity analysis.

Posterior Predictive Check

The final model parameter estimates, variance covariance matrix, and inter-patient variability estimates were used to perform simulations that predicted olanzapine concentrations at various olanzapine doses. The distributions of the predicted olanzapine

concentrations were compared to the observed concentrations for each study.

Final Pharmacokinetic Model

Two covariates, gender and body weight had a statistically significant influence on olanzapine pharmacokinetics and were retained in the final model. The effects of gender and body weight were on CL/F. Other patient specific factors such as age, race and smoking status did not have a significant influence on olanzapine pharmacokinetics although the C₁/F difference in adolescents due to smoking may have been confounded due to weight..

The following mean concentrations were observed in adolescents.

Olanzapine Concentration (ng/mL)					
Dose (mg)	N	n	Mean ± SD	(Minimum, Maximum)	
2.5	20	47	5.11±2.33	(0.290, 9.65)	
3.0	1	3	14.5±1.82	(13.11, 16.57)	
5.0	47	104	13.8±7.52	(0.890, 70.17)	
7.5	28	46	20.6±9.75	(4.41, 52.46)	
10.0	47	101	30.9±17.9	(3.18, 101.98)	
12.5	10	17	50.3±21.4	(23.86, 118.78)	
15.0	26	65	36.6±18.7	(2.56, 97.17)	
17.5	7	9	78.2±40.7	(37.14, 145.37)	
20.0	16	70	76.5±32.8	(11.36, 160.26)	

Abbreviations: N = number of patients, n = number of observations, SD = standard deviation.

Based upon the mean concentrations it appears that dose has no impact on the kinetics of Olanzapine in adolescents. The lack of a dose effect on pharmacokinetics was also observed in adults.

Parameter estimation results Final Model

Table HGMF.7.4. Pharmacokinetic Parameters for the Final Population Model

	Units	Estimate	%SEE	95 % CI
Pharmacokinetic model				
Absorption rate constant, K_a	hr ⁻¹	0.543 (Fixed)	-	-
Oral Clearance (CL/F) ^a	L/hr	13.6	6.16	(12.2 – 15.3)
Effect of gender on CL/F (Θ3) ^b	-	0.288	31.1	(0.127 – 0.477)
Effect of weight on CL/F (Θ4) ^{c,d}	1/kg	0.00585	34.4	(0.00248 – 0.00907)
Oral Volume of Distribution (V/F)	L	899	16.2	(687 – 1150)
Interpatient variability				
CL/F	%	40.5	19.7	-
V/F	%	65.4	47.2	-
Covariance between CL/F and V/F	-	0.232	31.8	-
Residual Error				
Proportional	%	27.1	14.2	-

Abbreviations: CI = confidence interval; SEE = standard error of the estimate.

^a CL_{female} = 13.6 L/hr.

^b CL_{male} = CL_{female} · (1 + Θ3) = 17.5 L/hr.

^c CL_{female at weight(w)} = 13.6 L/hr · e^[(Θ4)(w-70.1)]; where 70.1 is the median.

^d CL_{male at weight(w)} = 17.5 L/hr · e^[(Θ4)(w-70.1)]; where 70.1 is the median.

Goodness of fit

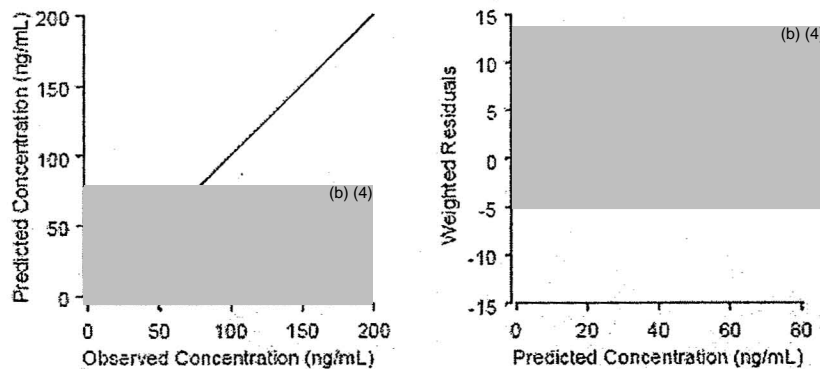
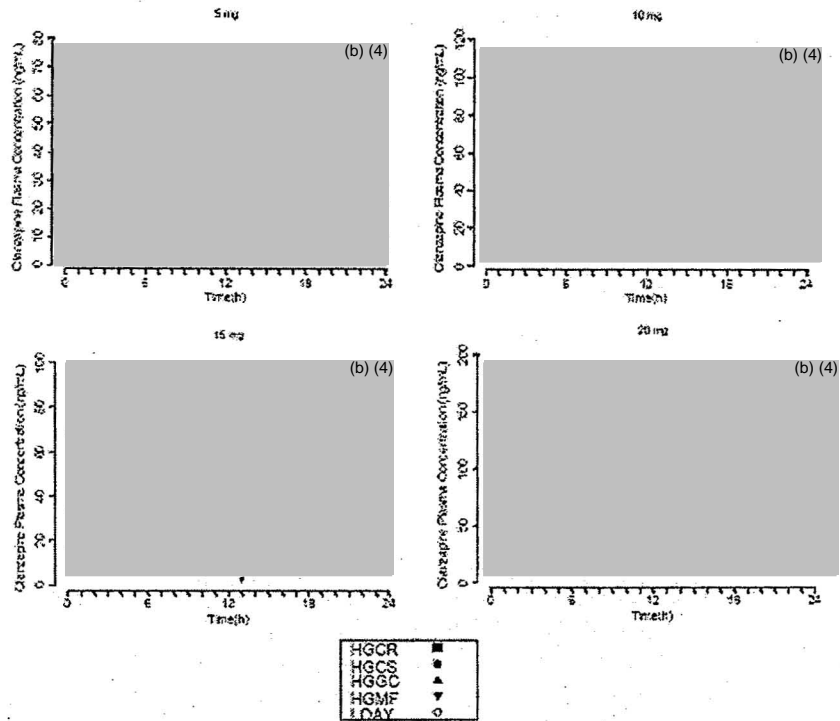


Figure HGMF.7.5. Goodness of fit plots for final model. Data from Studies HGCS, HGCR, HGGC, and HGMF.

Model Qualification

Posterior predictive check allowed for the comparison of the model predicted olanzapine concentrations with the observed olanzapine concentrations for each study. Most of the observed concentrations are within the model predicted concentration range (5th to 95th percentile) (Figure HGMF.7.7).



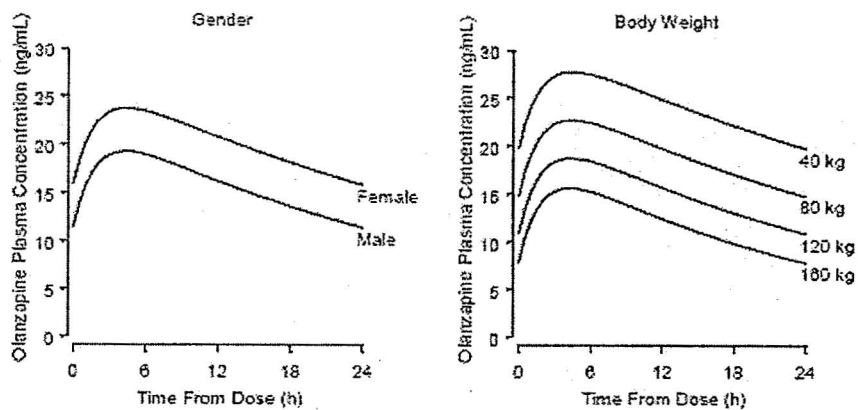
Note: Solid lines represent the 5th, 50th, and 95th percentile of the predicted olanzapine concentration-time profiles obtained simulating 1000 patients. Symbols represent observed olanzapine concentration.

Figure HGMF.7.7. Comparison of model predicted olanzapine concentration and observed olanzapine concentration by dose.

Overall Conclusions

Effects of Gender

Gender had a significant influence on CL/F. Inclusion of gender as a covariate reduced inter-patient variability from 45.9% to 40.5%. The CL/F of olanzapine in male patients is approximately 29% higher as compared with the female patients. Thus, on average, female patients receiving the same olanzapine dose as male patients are predicted to have approximately 29% higher steady state olanzapine concentrations. The predicted effect of gender on olanzapine concentrations for typical population is shown in(Figure HGMF.7.6).



Note: Gender: Predictions shown at the median body weight.
 Body weight: Predictions show the effect of body weight on a female patient.

Figure HGMF.7.6. Final population pharmacokinetic model. Predicted effect of covariates on plasma olanzapine concentrations at 10-mg olanzapine dose.

Variability in Olanzapine Pharmacokinetics

Variability in the final population pharmacokinetic model reflects the combination of inter-patient variability in pharmacokinetic parameters and intra-patient variability characterized by residual error. The interpatient variability in CL/F and V/F is 41% and 65%, respectively and the residual error is 27% (Table HGMF.7.4). The model predicted olanzapine concentrations at various doses of olanzapine are summarized in (Table HGMF.7.5). The maximal olanzapine concentration at steady state ($C_{max,ss}$) ranged from 7.81 ng/mL to 146 ng/mL (5th percentile after 5 mg to 95th percentile after 20 mg) in the dose range of 5 to 20 mg. The mean time of $C_{max,ss}$ was 6.6 hours. The minimal olanzapine concentration at steady state ($C_{min,ss}$) ranged from 5.51 ng/mL to 86.2 ng/mL (5th percentile after 5 mg to 95th percentile after 20 mg).

Table HGMF.7.5: Summary of Predicted Steady-state Olanzapine Concentrations Following Simulated Once-Daily Dosing

	$C_{min,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$t_{max,ss}$ (h)
5-mg			
Geometric Mean	16.6	10.8	6.55
Geometric CV%	49.7	43.1	7.38
5 th Percentile	7.81	5.51	5.79
50 th Percentile	16.7	10.8	6.56
95 th Percentile	36.4	21.5	7.37
10-mg			
Geometric Mean	33.3	21.7	6.55
Geometric CV%	49.7	43.1	7.38
5 th Percentile	15.6	11.0	5.79
50 th Percentile	33.5	21.6	6.56
95 th Percentile	72.8	43.1	7.37
15-mg			
Geometric Mean	49.9	32.5	6.55
Geometric CV%	49.7	43.1	7.38
5 th Percentile	23.4	16.5	5.79
50 th Percentile	50.2	32.4	6.56
95 th Percentile	109	64.6	7.37
20-mg			
Geometric Mean	66.6	43.3	6.55
Geometric CV%	49.7	43.1	7.38
5 th Percentile	31.2	22.0	5.79
50 th Percentile	66.9	43.2	6.56
95 th Percentile	146	86.2	7.37

Abbreviations: CV = coefficient of variation

Comparison of Adolescent and Adult Olanzapine Pharmacokinetics

(Study HGAJ, 912 patients) which was a study comparing Olanzapine and Haloperidol in the treatment of Schizophrenia.

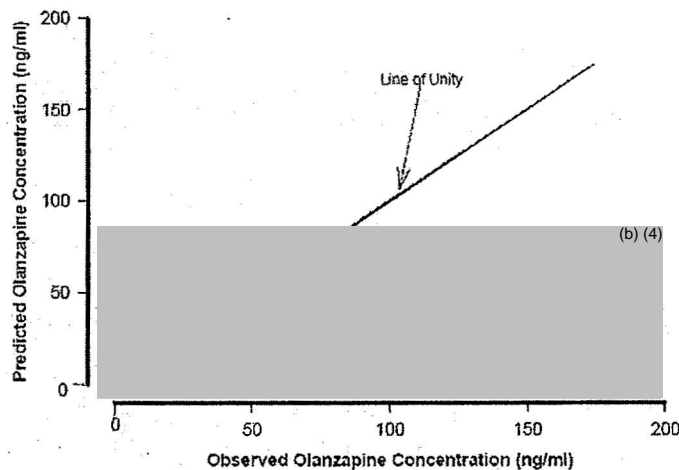
The results from study HGAJ is presented in the following Table: HGMF7.6

Table HGMF 7.6 Population pharmacokinetic parameters and 90% CI from adult study HGAJ

NONMEM Parameter Estimates		
Parameter	Parameter Value	95% Confidence Interval ^d
Cl ₁ ^a (L/hr)	13.50	12.61 - 14.39
Cl ₂ Male Smoker ^b (L/hr)	28.40	27.28 - 29.52
Cl ₂ Female Smoker ^b (L/hr)	23.06	22.15 - 23.97
Cl ₂ Male Nonsmoker ^b (L/hr)	18.01	16.86 - 19.15
Cl ₂ Female Nonsmoker ^b (L/hr)	12.01	11.35 - 12.68
V Male Smoker (L)	1360.0	1196.13 - 1523.87
V Female Smoker (L)	961.52	792.24 - 1130.80
V Male Nonsmoker (L)	918.00	801.92 - 1034.08
V Female Nonsmoker (L)	788.80	688.67 - 888.93
p ^c	0.731	0.679 - 0.783

a = Low clearance population
b = High clearance population
c = Fraction of patients in high clearance population
d = Determined from objective function mapping

Predicted vs Observed Olanzapine Concentrations Including The Extreme Outliers In The Final Model (Study HGAJ)



The firm compared the distributions of CL/F and V/F statistically using the Kolmogorov-Smirnov test, a nonparametric method. The test showed that were significantly different in adolescent and adult population ($p < .001$). The common area under the two distributions (adolescent and adult) of Figure HGMF.7.8 represents the proportion of patients having comparable values. Approximately 77% of the adolescent and adult patients had comparable CL/F estimates and approximately 69% of the patients had comparable V/F. The typical values (for example, geometric mean) of CL/F and V/F in adolescent patients are 21% and 17% lower than in adults. It should be noted that in adults, gender and smoking had a significant effect on CL/F and V/F while in

adolescents, gender and body weight had a significant effect. Thus, the effect of body weight on CL/F in adolescent patients and the high proportion of nonsmokers in adolescent patients (78% in adolescents versus 40% in adults) may explain the differences in oral olanzapine pharmacokinetics observed in these populations.

The observed steady state olanzapine concentrations in adolescent patients were also compared with those observed in adults (Study HGAJ). As noted above, the median steady state olanzapine concentrations in adolescent patients were slightly higher than those in adults at each dose (Figure HGMF.7.9). However, there is considerable overlap in the olanzapine concentration distribution in adolescents and adults. At 20 mg dose, olanzapine concentrations in a few adolescent patients exceeded the maximum concentration observed at 20 mg in adults. Steady state olanzapine concentrations in adolescent patients up to doses of 15 mg were encompassed within the range of olanzapine concentration (10th percentile after 5 mg and 90th percentile after 20 mg) reported in adults.

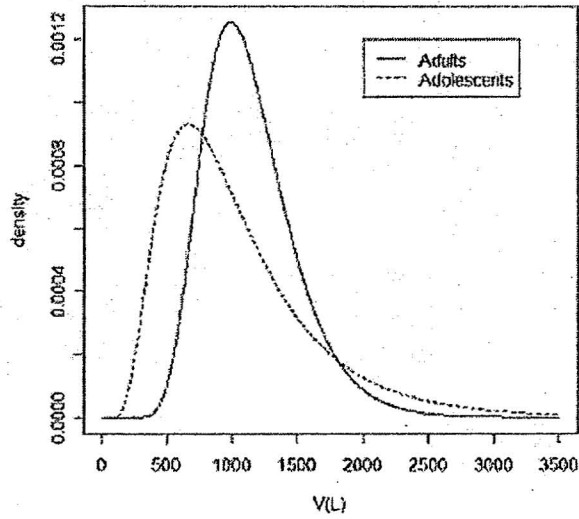
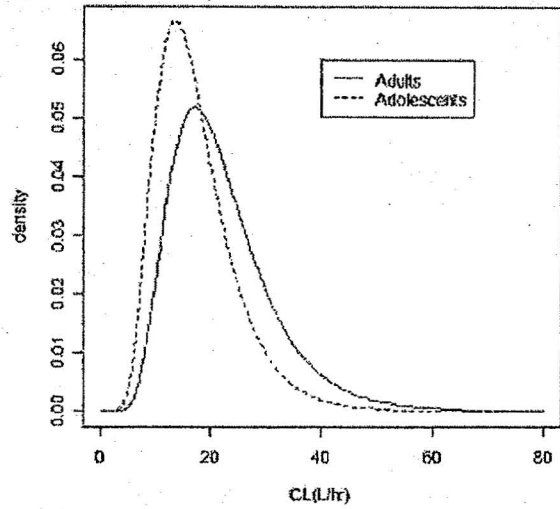
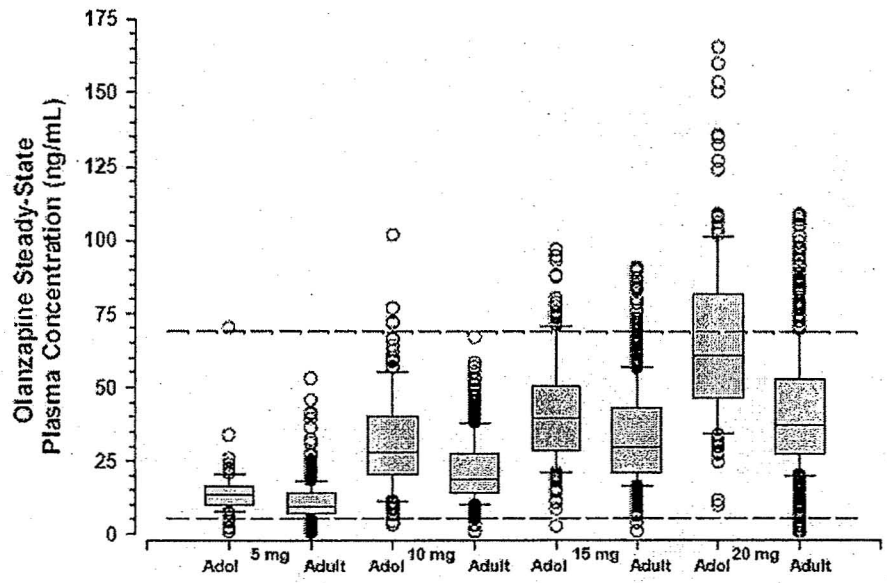


Figure HGMF.7.8. Distribution of individual olanzapine pharmacokinetic parameters (oral clearance and oral volume of distribution) in adult and adolescent patients.



Abbreviations: Adol = Adolescent

Note:

The middle line in each box plot represents the median; the top and bottom margins represent the 75th and 25th percentiles; the whiskers extend to the 90th and 10th percentiles; data points beyond the whiskers represent data in the tails of the distribution.

The dashed lines represent the 10th percentile of olanzapine concentration following 5-mg olanzapine daily and the 90th percentile of olanzapine concentration following oral 20-mg olanzapine daily in adults.

Figure HGMF.7.9.

Steady-state olanzapine plasma concentrations in adolescent and adult patients following oral olanzapine administration.

FDA RESULTS

BASE MODEL

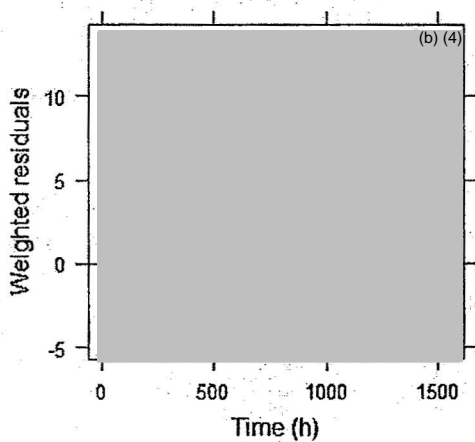
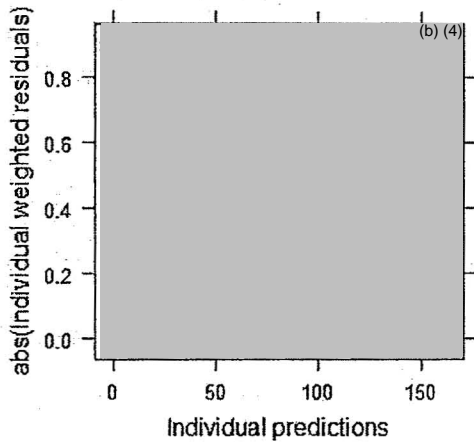
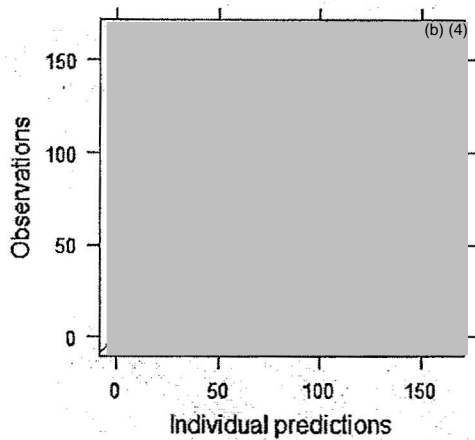
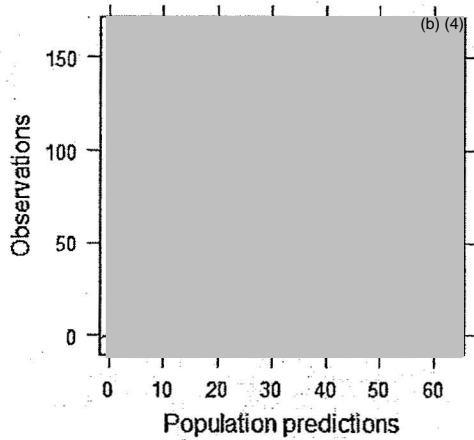


Table Summary of FDA Pharmacokinetic Parameters for the Base Population Model (Studies HGCS, HGCR, HGGC, HGMF)

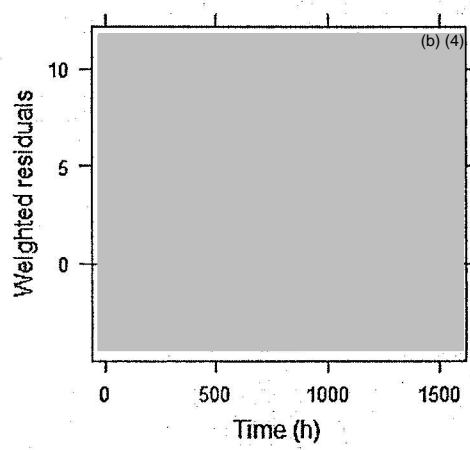
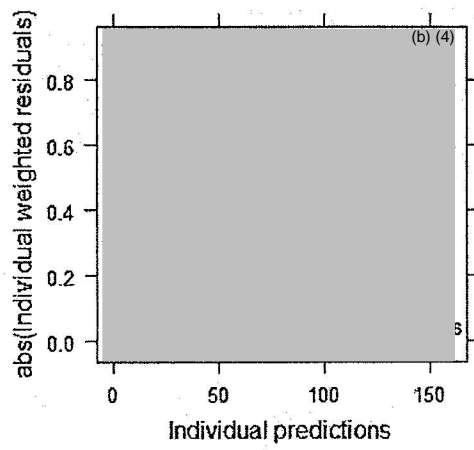
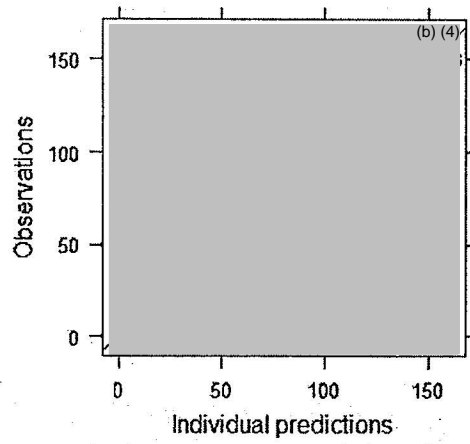
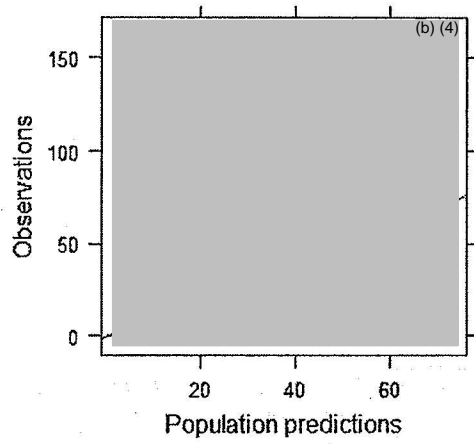
Units Estimate		%SEE
Pharmacokinetic Model		
Absorption rate constant, K_a hr ⁻¹	0.543 (Fixed)	-
Oral clearance, CL/F L/hr	16.3	4.61
Oral Volume of Distribution, V/F L	879	17.1
Interpatient Variability		
CL/F %	43.7	15.9
V/F %	62.2	42.3
Covariance between CL/F and V/F -	0.258	22.5
Residual Error		
Proportional %	27.0	13.7

Abbreviations: SEE = standard error of the estimate.

FDA Values all agree with sponsor for the Base model

Table Summary of FDA Pharmacokinetic Parameters for the Final Population Model (Studies HGCS, HGCR, HGGC, HGMF)

Units Estimate		%SEE
Pharmacokinetic Model		
Absorption rate constant, Ka hr ⁻¹	0.543 (Fixed)	-
Oral clearance, CL/F L/hr	13.66	456
Effect of Gender on CL/F	0.288	1191
Effect of Weight on CL/F	0.00585	80.7
Oral Volume of Distribution, L	899	993
Interpatient Variability		
CL/F %	38	401
V/F %	60	1291
Covariance between CL/F and V/F -	0.27	
Residual Error		
Proportional %	27	599
Abbreviations: SEE = standard error of the estimate.		



FDA's PROPOSED LABEL CHANGES

794 12.3 Pharmacokinetics

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents had a lower average body weight compared to adults, resulting in average olanzapine exposure that was approximately 30-63% higher in adolescents than adult patients.

Comments:

1. The base model results were consistent with those from the firm, however for the final model only the mean parameter values were in agreement. The variability of the data was much less with the firm's results. When OCP ran the control stream with WINGS OCP obtained a var/cov matrix file but when it was run under NMFE5 it terminated prior to the var/cov step. OCP was informed by the Pharmacometrics Division Director that computational differences were sometimes observed between different compilers and further resolution of the reason for the differences was not necessary.

2. Based upon visual comparison of the observed vs fitted graphs for studies HGAJ in adults and the current study, the graphical results indicate higher olanzapine levels in adolescents than in adults.

SIGNATURES

Andre Jackson _____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialized by Raman Baweja, Ph.D. _____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 20592, HFD-860(Mehta, Baweja, Jackson)
C:\Data\REVIEWS\NDA\ZYPREXA_NDA20-592-
SE5\POPPK\Zyprexpmreview.doc

References

Allerheiligen S, Cerimele B, Milosevich S, Johnson R, Nelson R, Tarassoff P. 1994. A population pharmacokinetic analysis of gemcitabine following variable length infusions. *Pharmaceutical Res* 11(10):S-377. Abstract 8178.

O'Brien L, Hewitt R, Heathman M, Ni L, Allerheiligen S. 1998. Challenging the robustness of a population pharmacokinetic model obtained from a phase III raloxifene study. In: *AAPS Pharm Sci* 1(1). Abstract 3548

Mandema JW, Verotta D, Sheiner LB. 1992. Building population pharmacokineticpharmacodynamic models. I. Models for covariate effects. *J Pharmacokinet Biopharm* 20(5):511-528.

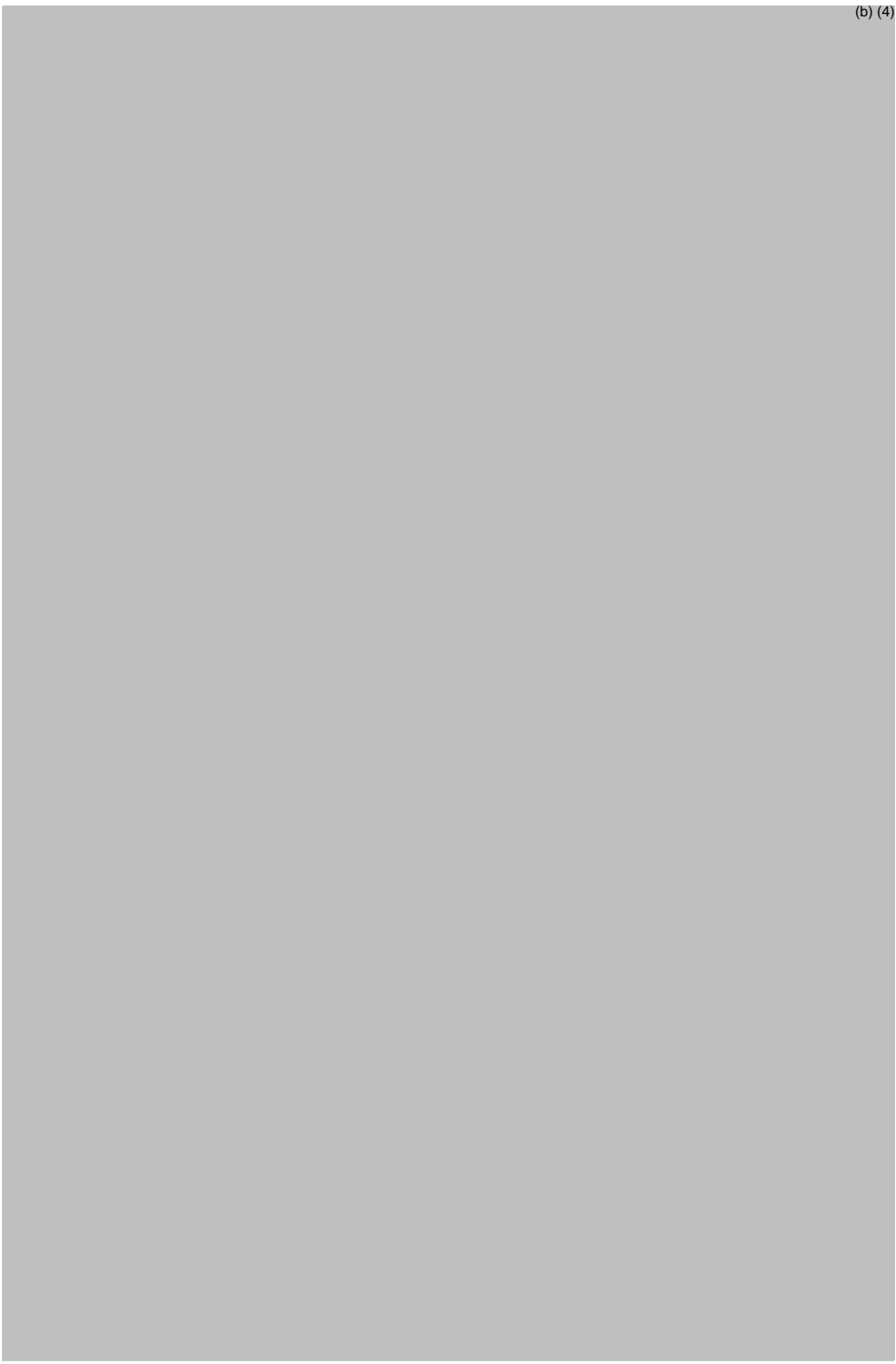
Appendix I**I. BASE MODEL CONTROL STREAM**



II. FINAL MODEL CONTROL STREAM



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this page is the manifestation of the electronic signature.**

/s/

Andre Jackson
3/27/2007 08:35:38 AM
BIOPHARMACEUTICS

Raman Baweja
3/27/2007 12:16:22 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020592 / S-035, 039, 040, 041, 049,053, 055

021086 / S-21, 031, 032, 034

021253 / S-037, 039, 043

OTHER REVIEW(S)

**REGULATORY PROJECT MANAGER
LABELING REVIEW**

Date: May 11, 2010
 DRUG/NDA: Zyprexa (olanzapine) Tablets (NDA 20592), Zydys ODT (NDA 021086),
 injection (NDA 021253)
 Sponsor: Eli Lilly
 Indications: Zyprexa Tablets, ODT, IM injection - Schizophrenia and Bipolar

Supplements:

21-253	S-039	PA	Zyprexa (olanzapine) Inj.	Revisions to laboratory and clinical findings	SDN 184, letter date 10/23/09
21-086	S-032	PA	Zyprexa Zydys (olanzapine) ODT	Revisions to laboratory and clinical findings	SDN 176, letter date 10/23/09
20-592	S-053	PA	Zyprexa (olanzapine) Oral Tablets	Revisions to laboratory and clinical findings	SDN 418, letter date 10/23/09

REVIEW

Reviewed by Medical Officer: Yes.

The supplements listed above provide for revisions to section 6.2, Vital Signs and Laboratory Studies, of the label. The previously approved label, approved 1/27/10 (NDA 20592 S-052, NDA 21086 S-031, and NDA 21253 S-037), provided for changes to section 5.15, Hyperprolactinemia - these supplements add nothing more than the proposed changes listed below. The medical officer's review concurs with all changes as proposed by the sponsor.

These supplemental applications provide for the following changes to product labeling:

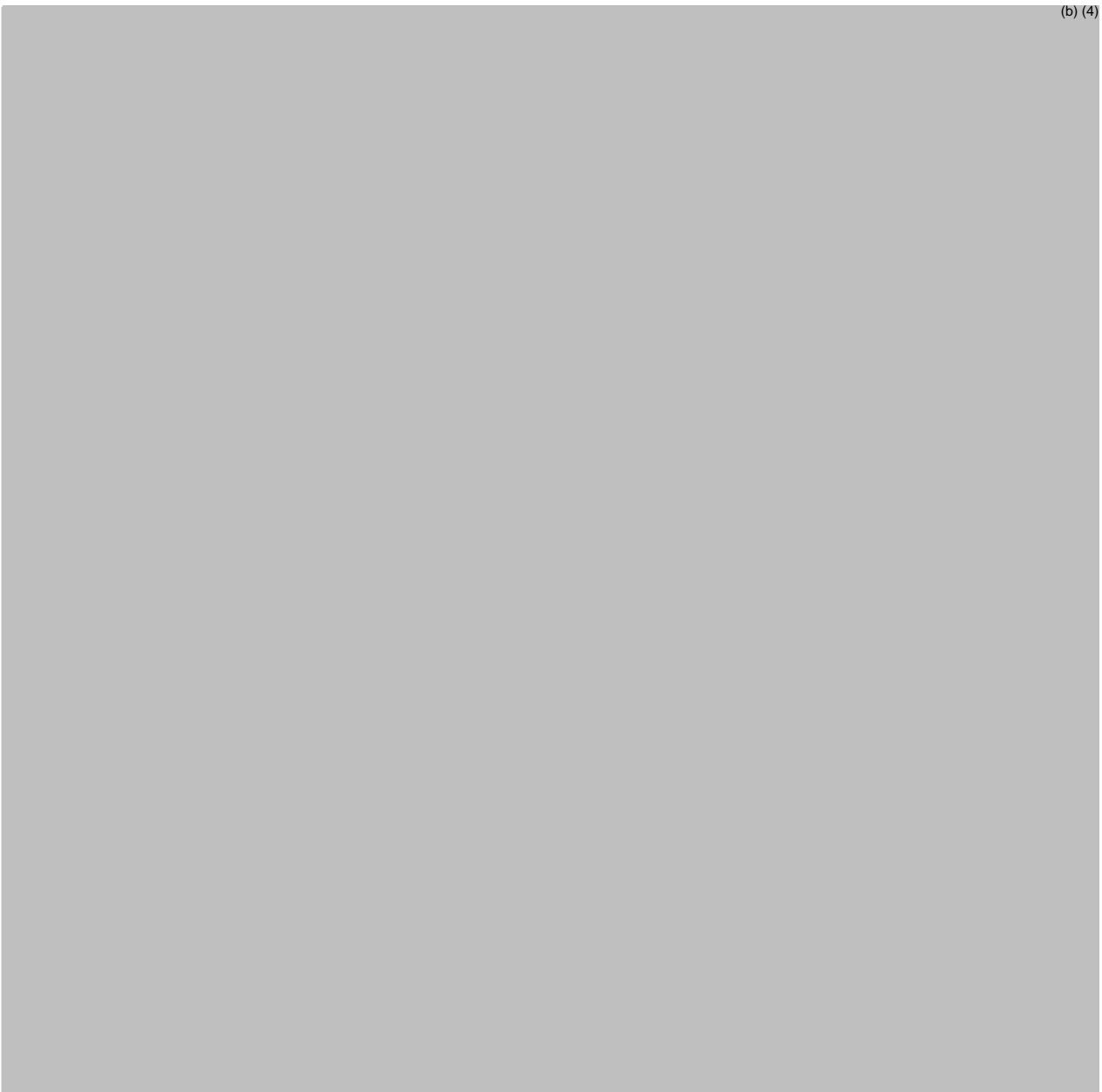
6.2 Vital Signs and Laboratory Studies

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials [see *Warnings and Precautions (5)*].

(b) (4)

NDA 020592 S-053
NDA 021086 S-032
NDA 021253 S-039
Page 2

(b) (4)



{See appended electronic signature page}

Keith Kiedrow, Pharm.D., Team Leader, Senior Regulatory Project Manager

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-53	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-21253	SUPPL-39	ELI LILLY AND CO	ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ
NDA-21086	SUPPL-32	ELI LILLY AND CO	ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS

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/s/

KEITH J KIEDROW
05/27/2010

**REGULATORY PROJECT MANAGER
LABELING REVIEW**

Date: January 26, 2010
 Drug/NDA: Zyprexa (olanzapine) & Symbyax (olanzapine/fluoxetine)
 Sponsor: Lilly
 Indication: Schizophrenia; Treatment Resistant Depression
 Supplements:

NDA	Supplement	Dated	Action
Symbyax (olanzapine/fluoxetine) ; NDA 21-520			
21-520	S-022	8-3-09	Approved 8-31-09
21-520	S-023	9-1-09, and amended on 9-18-09	Open
Zyprexa (olanzapine) Tablets ; NDA 20-592			
20-592	S-040/S-041	8-3-09	Approved 12-4-09
20-592	S-052	9-1-09, and amended on 9-18-09, 10-6-09, and 12- 16-09	Open
Zyprexa (olanzapine) ODT ; NDA 21-086			
21-086	S-030	8-3-09	Approved 8-31-09
21-086	S-031	9-1-09, and amended on 9-18-09, 10-6-09, and 12- 16-09	Open
Zyprexa (olanzapine) Injection ; NDA 21-253			
21-253	S-036	8-3-09	Approved 8-31-09
21-253	S-037	9-1-09, and amended on 9-18-09, 10-6-09, and 12- 16-09	Open

Materials Reviewed

1. Last approved labelings attached to approval letters dated 8-31-09, and 12-4-09.
2. Medical officer review of supplements.
3. Correspondence to sponsor regarding labeling negotiations.

Zyprexa Labeling Changes

- Revisions to Section 5.14 (Hyperprolactinemia)

Symbyax Labeling Changes

- Revisions to Section 5.20 (Hyperprolactinemia)

- Revisions to Section 6.2 (Vital Signs and Laboratory Studies) regarding an increase in creatinine phosphokinase.

Review

- Both the Zyprexa and Symbyax labeling supplements, submitted as “Prior Approval” applications were amended to provide for updated language secondary to Agency approval actions on separate applications. For Symbyax, the labeling was amended to include the leukopenia class labeling language (approved on 8-31-09). For Zyprexa, the labeling was updated to include both the leukopenia class labeling language as well as the pediatric approval (Agency action letters dated 8-31-09, and 12-4-09, respectively).
- The clinical team requested revisions to the sponsors’ proposed labeling in order to secure labeling agreement at the team leader level, and this was conveyed to the sponsor in an e-mail dated 1-12-10. Lilly submitted a counterproposal in an e-mail dated 1-14-10 which was found to be acceptable to the clinical team.

CONCLUSIONS

1. The supplement only provides for changes when compared to the last approved labeling (see attached labeling comparing proposed labeling to last approved labeling).
2. The clinical team concurs with the sponsor’s counterproposal.
3. I recommend that an approval letter issue for these supplemental applications.

{See appended electronic signature page}

Paul David, CPMS

Attachment

- 1) 1-12-10 e-mail
- 2) 1-14-10-e-mail
- 3) Annotated labeling denoting revisions when compared to the last approved labeling

David, Paul A

From: David, Paul A
Sent: Tuesday, January 12, 2010 2:32 PM
To: 'phillipsch@lilly.com'; 'usher_roland_w@lilly.com'
Cc: Kiedrow, Keith
Subject: Zyprexa and Symbyax Prior Approval Labeling Supplements

Good Day Christine and Roland,
Please refer to your submissions dated 9-1-09, providing for Prior Approval labelings supplements submitted to the Zyprexa (NDA 20-592/S-052, 21-086/S-0031 & 21-253/S-037) and Symbyax (NDA 21-520/S--23) applications.

We have completed our review of your supplements, and we would like to negotiate labeling so that a final action can be taken on these pending supplements. Please review our revisions, below, and let me know if they are acceptable.

Thanks,
Paul
CAPT Paul A. David, R.Ph.
Chief, Project Management Staff
Division of Psychiatry Products/HFD-130
Food and Drug Administration
10903 New Hampshire Avenue, Building 22, Room 4100
Silver Spring, Maryland 20993-0002
Phone: 301-796-1058
Fax: 301-796-9838
paul.david@fda.hhs.gov

Yellow highlights represent Lilly's proposed changes/deletions, and blue font represents the Agency's revisions

Symbyax



(b) (4)

(b) (4)

Zyprexa

(b) (4)

David, Paul A

From: Christine Ann Phillips [PHILLIPS_CHRISTINE_ANN@LILLY.COM]
Sent: Thursday, January 14, 2010 4:30 PM
To: David, Paul A
Cc: Kiedrow, Keith; phillipsch@lilly.com; usher_roland_w@lilly.com
Subject: Re: Zyprexa and Symbyax Prior Approval Labeling Supplements

Attachments: Zyprexa and Symbyax USPI Text to FDA (14Jan2010).docx



Zyprexa and
ymbyax USPI Text .

Hi Paul,

We accept the majority of changes suggested by FDA. We propose a couple of modifications to the footnotes, as shown in the enclosed document. Reasons are provided in comments. Thank you for the acceptance of the creatine phosphokinase language in the Symbyax USPI. Please let me know if you'd like to discuss further.

In addition, I'd like to ask

(b) (4)

Regards,
Christine

(See attached file: Zyprexa and Symbyax USPI Text to FDA (14Jan2010).docx)

Christine Phillips, PhD, RAC
Eli Lilly and Company
US Regulatory Affairs
317.276.7239 (office)
317.625.6045 (mobile)
phillipsch@lilly.com

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"David, Paul A"
<Paul.David@fda.hhs.gov>
To
<phillipsch@lilly.com>,
01/12/2010 02:31 PM <usher_roland_w@lilly.com>
cc
"Kiedrow, Keith"
<Keith.Kiedrow@fda.hhs.gov>
Subject
Zyprexa and Symbyax Prior Approval
Labeling Supplements

Good Day Christine and Roland,
Please refer to your submissions dated 9-1-09, providing for Prior Approval labelings supplements submitted to the Zyprexa (NDA 20-592/S-052, 21-086/S-0031 & 21-253/S-037) and Symbyax (NDA 21-520/S--23) applications.

We have completed our review of your supplements, and we would like to negotiate labeling so that a final action can be taken on these pending supplements. Please review our revisions, below, and let me know if they are acceptable.

Thanks,
Paul
CAPT Paul A. David, R.Ph.
Chief, Project Management Staff
Division of Psychiatry Products/HFD-130
Food and Drug Administration
10903 New Hampshire Avenue, Building 22, Room 4100 Silver Spring, Maryland 20993-0002
Phone: 301-796-1058
Fax: 301-796-9838
paul.david@fda.hhs.gov

Yellow highlights represent Lilly's proposed changes/deletions, and blue font represents the Agency's revisions

Symbyax

(b) (4)



Proposed Labeling Changes for Creatine phosphokinase [These changes are acceptable.]

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs.

An increase in creatine phosphokinase has been reported very rarely in SYMBYAX-treated patients and infrequently in clinical trials of olanzapine treated patients.

Zyprexa

As with other drugs that antagonize dopamine D2 receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats [see Nonclinical Toxicology (13.1)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.



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Zyprexa USPI – Proposed Changes from Eli Lilly and Company (14 January 2010)

5.15 Hyperprolactinemia



(b) (4)

Symbyax USPI – Proposed Changes from Eli Lilly and Company (14 January 2010)

(b) (4)





66 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-52	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-21520	SUPPL-23	ELI LILLY AND CO	SYMBYAX
NDA-21086	SUPPL-31	ELI LILLY AND CO	ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS
NDA-21253	SUPPL-37	ELI LILLY AND CO	ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ

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/s/

PAUL A DAVID
01/26/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 1, 2009

To: Thomas Laughren, MD, Director
Division of Psychiatry Products (DPP)

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management (DRISK)

LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Product Information Reviewer, Acting Team Leader
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Product Information Reviewer, Acting Team
Leader
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide),

Drug Name(s): Zyprexa (olanzapine) Tablet and Zyprexa Zydys (olanzapine)
Tablet, Orally Disintegrating

Application Type/Number: NDA 20-592

Submission Number: S-040 and S-041

Applicant/sponsor: Eli Lilly and Company

OSE RCM #: 2009-1412