The following information has been compiled from the Olanzapine NDA (New Drug Application) Integrated Summary of Safety Report (filed with FDA September 1995):

Frequent, Infrequent, and Rare Treatment-Emergent Adverse Events

Treatment-emergent adverse events reported by olanzapine-treated patients in the studies included in the integrated primary safety database are listed below by body system and classified as frequent, infrequent, or rare events. Events were classified using the following definitions: frequent adverse events were defined as those occurring in at least 1/100 patients, infrequent adverse events were defined as those occurring in less than 1/100 to at least 1/1,000 patients, and rare events were defined as those occurring in less than 1/1,000 patients.

Endocrine System--*Infrequent:* **diabetes mellitus**, prolactin increased, goiter; *Rare:* ***diabetic acidosis***.

Metabolic and Nutritional Disorders--*Frequent:* weight gain, SGPT increased, creatine phosphokinase increased, peripheral edema, weight loss; ***Infrequent***: edema, SGOT increased, ***hyperglycemia***, dehydration, alcohol intolerance, bilirubinemia, ***acidosis***, hyponatremia, hypokalemia, ***hypoglycemia***, alkaline phosphatase increased, hyperkalemia, hyperuricemia, iron deficiency anemia, ketosis, water intoxication; *Rare:* hypercholesteremia, hyperlipemia, BUN increased, creatinine increased, electrolyte abnormality, generalized edema, gout, hypochloremia, hypoproteinemia.

Urogenital System--*Frequent:* dysmenorrhea, urinary tract infection, urinary incontinence, metrorrhagia, hematuria, menstrual disorder, vaginitis; ***Infrequent:*** unintended pregnancy, impotence, amenorrhea, dysuria, urinary frequency, pyuria, menorrhagia, cystitis, urinary retention, breast pain, prostatic disorder, urination impaired, urine abnormality, uterine fibroids enlarged, ***glycosuria***, polyuria, abnormal ejaculation, female lactation, urinary tract disorder, abortion, endometrial disorder, fibrocystic breast, leukorrhea, menopause, ovarian disorder, uterine hemorrhage, vaginal hemorrhage, vaginal moniliasis, vulvovaginitis; *Rare:* albuminuria, balanitis, epididymitis, gynecomastia, penis disorder, priapism, anorgasmia, bilirubinuria, bladder neoplasm, breast carcinoma, breast enlargement, breast neoplasm, hydronephrosis, kidney calculus, oliguria, pyelonephritis, urea clearance decreased, urethral pain, urinary urgency, urolithiasis.

A summary of baseline-to-endpoint change for each clinical chemistry analyte is presented in Table 14 by treatment group. Statistically significant differences between the treatment groups were observed in change from baseline to endpoint for **nonfasting glucose** (olanzapine, 0.17 mmol/L; haloperidol, -0.88 mmol/L), uric acid (olanzapine, 41.98 mmol/L; haloperidol, 1.81 mmol/L), and potassium (olanzapine, -0.06 mmol/L; haloperidol, 0.15 mmol/L). **Because the haloperidol treatment group had a greater change than the olanzapine treatment group, the treatment differences observed with nonfasting glucose and potassium were not considered clinically significant.**

Table 1. Criteria for Identifying Patients with Potentially Clinically Significant Change in Clinical Chemistry Analytes

Analyte	Unit	Low	High
Glucose (nonfasting)	mmol/L	2.4975	13.875

Table 2. Criteria for Identifying Patients with Potentially Clinically Significant Change in Urinary (UA) Analytes

Analyte	Low	High
UA-Ketones		increase ≥2 and score ≥3
UA-Glucose		increase ≥2 and score ≥3

Table 3. Adverse Events Reported as Reason for Discontinuation Active-Controlled Integrated Database Acute Phase

Event Classification	Olanzapine (N=1796) n (%)	Haloperidol (N=810) n (%)	Fisher's Exact p-Value
Diabetes Mellitus	1(0.1)	0(0)	1.00

Table 4. Incidence of High or Low Clinical Chemistry Analytes at Any Time Placebo-Controlled Integrated Database Acute Phase

Clinical Chemistry		Olz			Placebo			Fisher's Exact	Cochran-Mantel-Haenszel
		N	n	%	N	n	%	P-value	P-value
Name of Lab Test	Direction								
GLUCOSE, NON-FASTING	High	243	3	1.2%	115	2	1.7%	.658	.827
	Low	229	8	3.5%	112	8	7.1%	.172	.146

Table 5. Treatment-Emergent Adverse Events Active-Controlled Integrated Database Acute Phase

Event Classification	Olanzapine (N=1796) n (%)	Haloperidol (N=810) n (%)	Cochran-Mantel-Haenszel p-Value	Fisher's Exact p-Value
Glycosuria	2 (0.1)	0	0.371	1.000
Acidosis	4 (0.2)	0	0.181	0.317
Hypoglycemia	0	2 (0.2)	0.044	0.097
Diabetes Mellitus	3 (0.2)	1 (0.1)	0.731	1.000

Note: The Cochran-Mantel-Haenszel test indicated a greater incidence of incoordination, colitis, hypoglycemia, and reflexes increased as a reported event in haloperidol-treated patients than in olanzapine-treated patients.

Table 6. Incidence of Abnormal, High, or Low Urinary Analytes at Any Time Active-Controlled Integrated Database Acute Phase

Urinalysis		Olz			Hal			Fisher's Exact	Cochran-Mantel-Haenszel
		N	n	%	N	n	%	P-value	P-value
Name of Lab Test	Direction								
UA-GLUCOSE	Abnormal	1659	80	4.8%	740	24	3.2%	.083	.073
UA-KETONES	Abnormal	1485	199	13.4%	668	95	14.2%	.635	.992

Table 7. Treatment-Emergent Adverse Events
F1D-MC-HGAO Acute Phase

Event Classification	Olanzapine (N=120) n (%)	Placebo (N=118) n (%)	Fisher's Exact p-Value
Acidosis	1 (0.8)	0	1.000
Hypoglycemia	0	1 (0.8)	0.496
Diabetic mellitus	1 (0.8)	1 (0.8)	1.000

Table 8. [[Insert Table LABT21GC, LABT21GC, Incidence of High or Low Clinical Chemistry Analytes at Any Time F1D-MC-HGAO Acute Phase

Clinical Chemistry		Olz			Placebo			Fisher's Exact
Name of Lab Test	Direction	N	n	%	N	n	%	P-value
GLUCOSE, NON-FASTING	High	110	1	0.9%	112	0	0.0%	.495
	Low	93	19	20.4%	101	19	18.8%	.857

Table 9. Incidence of Abnormal, High, or Low Urinary Analytes at Any Time F1D-MC-HGAO Acute Phase

Urinalysis		Olz			Placebo			Fisher's Exact
Name of Lab Test	Direction	N	n	%	N	n	%	P-value
UA-GLUCOSE	Abnormal	98	8	8.2%	107	10	9.3%	.809
UA-KETONES	Abnormal	76	29	38.2%	88	36	40.9%	.751

Table 10. Incidence of High or Low Clinical Chemistry Analytes
F1D-MC-HGAJ Acute Phase

Clinical Chemistry		Olz			Hal			Fisher's Exact
		N	n	%	N	n	%	P-value
Name of Lab Test	Direction							
GLUCOSE, NON-FASTING	High	43	0	0.0%	15	0	0.0%	n/a
GLUCOSE, NON-FASTING	Low	40	4	10.0%	14	1	7.1%	1.00

Table 11. Incidence of Abnormal, High, or Low Urinary Analytes at Any Time, Patients ≥65 Years of Age
F1D-MC-HGAJ Acute Phase

Urinalysis		Olz			Hal			Fisher's Exact
		N	n	%	N	n	%	P-value
Name of Lab Test	Direction							
UA-GLUCOSE	Abnormal	41	3	7.3%	15	1	6.7%	1.00

Table 12. Treatment-Emergent Adverse Events in
Olanzapine-Treated Patients Overall Integrated Database

Event Classification	Olanzapine (N=2500) n (%)
Acidosis	7 (0.3)
Hypoglycemia	4 (0.2)
Diabetic acidosis	1 (0.0)
Diabetes Mellitus	16 (0.6)
Glycosuria	5 (0.2)

Table 13. Adverse Events Reported as Reason for Discontinuation in Olanzapine-Treated Patients Overall Integrated Database

Event Classification	Olanzapine (N=2500) n (%)
Patients Discontinued	372 (14.9)
Hypoglycemia	1 (0.0)
Diabetes mellitus	1 (0.0)

Table 14. Clinical Chemistry Analytes, Mean Change from Baseline to Endpoint, Patients ≥65 Years of Age
F1D-MC-HGAJ Acute Phase

				Baseline		Change to Endpoint		p-Values
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	
NFGLU	mmol/L	Olz	44	6.08	2.13	0.17	1.56	.024
		Hal	15	6.36	1.38	-0.88	1.36	

Reporting SI units
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.
Note: Models:
FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
XLAS0006
Legend of Lab Test Code Abbreviations:

Abbrev.	Description
NFGLU	GLUCOSE, NON-FASTING

June 20, 1997

Dr. Brad Spellberg
c/o Dr. Donna Wirshing
VA Medical Center
West Los Angeles, Brentwood Division
11301 Wilshire Blvd., Bldg. 210
Los Angeles, CA 90073

Dear Dr. Spellberg,

I have enclosed information on the incidence of diabetes and related parameters in olanzapine treatment from the olanzapine integrated summary of safety report. These data were part of the olanzapine NDA submission to the FDA in September of 1995 and were gathered from global clinical trials. I hope that these data are valuable to your research.

If you require further information please contact me at (317) 277-6161 or *j.ramsey@lilly.com*.

Sincerely,

Jeffrey T. Ramsey
Zyprexa Product Team

cc: encl