APPENDIX 7
Review of Blood Sugar Alterations

Review of Commercially Marketed (Spontaneous) Olanzapine and Blood Sugar Alterations Adverse Event Reports

October, 1997

1. Introduction

In response to a query from South Africa, a review was undertaken of all spontaneous adverse event reports/patient cases for olanzapine where a COSTART (dictionary of terms used to encode adverse events) Event Term, used to describe a clinical event in the report/cases, potentially reflected an alteration in blood sugar. The terms evaluated were hyperglycemia, hypoglycemia, diabetic coma, diabetic acidosis, and diabetes mellitus. These events occurred in temporal association with the administration of or following the administration and discontinuation of olanzapine. The occurrence of these events does not imply that olanzapine is an etiologic contributor to the events. Many alternative etiologies may be responsible for these events. The Drug Experience Network system (DEN) is the electronic system used by Lilly to capture all spontaneous and serious clinical trial adverse event data received for Lilly products. DEN was searched for spontaneous reports/cases up to an endpoint date of August 31, 1997.

Fifty-seven reports/patient cases, reporting 69 events(events voluntarily reported to Eli Lilly and Company which were observed in patients being treated with a commercially marketed pharmaceutical product) potentially reflecting an alteration in blood sugar were entered into and maintained in the DEN.

Event	# Of Times Event Was Reported	# Of Reports/Patient Cases Represented
Hyperglycemia	54	54 reports
Hypoglycemia	6	3 unique reports and 3 with hyperglycemia reports
Diabetes mellitus (DM)	4	all with hyperglycemia reports
Diabetic coma	1	all with a hyperglycemia report
Diabetic acidosis	4	all with hyperglycemia reports
TOTALS	69	57 reports

Weight gain as a COSTART Event Term was also considered to determine whether there was a correlation between weight gain and hyperglycemia in the olanzapine reports. However, in only two of the 237 times weight gain was used as a COSTART Event Term was it involved in a blood sugar alteration report.

1.1. DEN REPORTS

1.1.1. Definitions/Conventions

Term	Definitions
Mfr. Report #	The unique identification number for a report that is assigned by DEN when an adverse event is reported to Lilly and entered into the system.
Age	The age of the patient at the time of the event.
Sex	The sex of the patient.
Diabetic History	Any significant history of diabetes.
Peak BS or Lowest BS	The peak blood sugar or the lowest blood sugar. Mmol/L blood glucose converts to mg % blood glucose by using a factor of 18 (mmol/L x 18 = mg %). All report information has been converted to mg % blood sugar for consistency and ease of comparison.
$HgbA_{1C}$ value	Hemoglobin A_{1C} (Conventional Units: %)
Dose	The dose of olanzapine the patient was on at the time of the decrement.
Duration	The period of time the patient was on olanzapine up to the date of the first significant blood sugar value was noted.
Concomitant Medications	All concomitant systemic medications that the patient was taking at the time or shortly before the onset of the event.
Comment	Any history that may be pertinent to understanding the event.
NA	Not applicable
NR	Not reported
DM	Diabetes Mellitus
IDDM	Insulin dependent diabetes mellitus
NIDDM	Non-insulin dependent diabetes mellitus
FBS	Fasting blood sugar
BS	Blood sugar
CHO	Carbohydrate

1.1.2. Reports of (Spontaneous) Blood Glucose Alterations associated with Commercially Marketed Olanzapine

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
1	CA97064522A	22	M	Hyperglycemia Polyuria Polydipsia	NIDDM History	FBS=310mg% and random BS= 485mg%	none	5mg BID	20 days for FBS and 27 days for random BS	clonaz venlaf olanza
2	CL97075797A	30	F	Hyperglycemia Weight Gain Increased Appetite Dyspnea, Somnolence Manic Reaction Lack of drug effect	No History	unknown; report states BS is 1500% above normal	none	5mg daily and reduced to 2.5mg daily due to weight gain	BS noted to be elevated upon admission to hospital 6 months after starting olanzapine.	fluoxet oral hy (name
3	DE97082419A	51	M	Hyperglycemia	No History	Prior to breakfast = 300mg%; after breakfast = 90mg% and after lunch = 50mg%	none	unknown	unknown	unkno

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
4	ES97071102A	34	F	Hyperglycemia	IDDM	600 without units	none	20mg daily	10 weeks	insulin
5	ES97072179A	34	F	Hyperglycemia	IDDM	400mg%	none	unknown	3 days	regula diazep sulpiri pyrido
6	GB97012851A	NR	M	Hyperglycemia Hypertension	No History	198mg%	none	10mg daily	2 days: events started prior to olanzapine treatment	lorazep droper atenol amlodi
7	GB97062119A	62	M	Hyperglycemia	NIDDM	180mg%	none	10mg daily	6 months	gliben
8	US96114288A	45	M	Hyperglycemia	NIDDM	unknown	none	10mg daily	unknown	fluvast diphen valpro glybur
9	US96121894A	NR	F	Hypoglycemia Hypotension Coma	unknown	unknown	none	5mg daily	1 day	clozap phenyt lithiun ranitid
10	US96123052A	46	F	Hyperglycemia	unknown	BS = 230mg% on Oct-15-96 and FBS is 600mg% on Dec-09-96	none	10mg daily	60 days prior to Dec-09-96 reading of 600mg%	ensure supple
11	US96123673A	75	M	Hyperglycemia Diabetes Mellitus	No History	560mg%	none	5mg daily	23 days	risperi paroxe
12	US96123925A	43	F	Hyperglycemia	No History	157mg%; baseline BS was 85mg% 5 weeks prior to peak BS	none	7.5mg TID	30 days prior to peak BS	carban ranitid furose clonaz

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
										venlafa potassi nadolo
13	US96124591A	78	M	Hyperglycemia	No History	Peak random BS = 560mg% with baseline value of 200mg%	none	5mg daily	14 days	unkno insulin hyperg

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
14	US97011171	34	M	Hyperglycemia Diarrhea Dehydration Malaise Convulsion	No History	Random BS: 1400mg%	none	7.5mg daily	6 weeks	lithium
15	US97012470A	65	F	Hyperglycemia	No History	Random BS = 400mg%	none	10mg daily	60 days	thiothi aspirin furose digoxi trihexy
16	US97014858A	NR	NR	Hyperglycemia	No History	FBS= >200mg%	none	unknown	unknown	none
17	US97014882A	33	M	Hyperglycemia Nausea Hypercholesteremia	No History	Random BS = 500mg%	none	10mg daily	5 weeks	zolpide potassi clonaz indapa fluvast felodip mirtaz

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
18	US97015026A	NR	NR	Hyperglycemia	IDDM	unknown	none	unknown	unknown	insulin
19	US97021057A	40	F	Hyperglycemia Diabetic coma Diabetic acidosis Fever Asthenia Dehydration Hypotension Kidney Function Abnormal NMS	undiagnosed diabetic (see HgbA1C)	1400mg%	12.3	10mg daily	20 days	carban lithium levothy atenolo trazodo alprazo halope spirono althiaz
20	US97021303A	48	M	Hyperglycemia Somnolence Emotional Lability	NIDDM	225mg%	none	5mg daily	10 days	glybur acetam
21	US97022137A	17	M	Hyperglycemia	IDDM	Random BS= 300mg%	none	5mg BID	14 days	nefazo insulin valpro fluvox benztro
22	US97022578A	45	M	Hyperglycemia Ketosis Coma Fever	No History	Upon admit to hospital: 900mg%	none	20mg daily	unknown	chlorpr lorazep lithium

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
23	US97022638A	59	F	Hyperglycemia Polyuria Polydipsia Weight Gain	No History	Upon admit to hospital: 700mg% (FBS 6 days prior to start of olanzapine= 218mg%	none	15mg daily	30 days	amlodi furose (risper lithiun stoppe
24	US97022944A	NR	M	Hyperglycemia	IDDM	unknown	none	unknown	unknown	insulin
25	US97024867A	49	M	Hyperglycemia	NIDDM	random BS > 300mg%	none	unknown	3 weeks	glybur allopu clonaz thiorid spiron labetal potassi bumet fluoxet
26	US97030154A	72	F	Hyperglycemia	NIDDM (6 yrs duration)	random BS = 524mg%	none	7.5mg daily	20 days	halope

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
27	US97031054A	65	F	Hyperglycemia Anemia Hypokalemia Intentional Overdose (30mg daily)	NIDDM	unknown	none	10mg TID (30mg/day)	25 days	perphe regula NPH i
28	US97031177A	NR	NR	Hyperglycemia Elevated Pancreatic Enzymes	unknown	unknown	unknown	unknown	unknown	unkno
29	US97031237A	54	M	Hyperglycemia Drug Interaction	NIDDM	random BS = 230mg%	none	7.5mg daily	60 days	glipizi trihexy
30	US97031381A	42	F	Hyperglycemia Pancreatitis Fever Sepsis Amylase increased Somnolence Stupor	No History	random BS = 1672mg%	none	20mg daily	14 days	thiothi clonaz valpro

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
31	US97033103A	37	F	Hyperglycemia	NIDDM	random BS = 304mg%	none	10mg daily	30 days	clozap clonaz benztr insulin
32	US97033517A	50	F	Hyperglycemia	NIDDM	random BS = 359mg%	none	unknown	60 days	insulin sliding BS
33	US97034576A	NR	M	Hyperglycemia	NIDDM	unknown other than “spiked” a BS	none	unknown	unknown	clonaz nifedip
34	US97035644A	79	F	Hyperglycemia	NIDDM	random BS = >300mg% at multiple times	7.6	unknown	30 days	lente i pravas risperi phenel thyroi

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
35	US97041084A	21	F	Hyperglycemia	No History	FBS= 270mg% and bedtime (HS) sugar = 400mg%	none	20mg daily	8 weeks	valpro trihexy paroxe thyroic
36	US97043244A	43	M	Drug Level Increased Schizophrenic Reaction Creatinine Phosphokinase increased SGOT increased SGPT increased Alkaline phosphatase increased Tremor Agitation Speech disorder Hypernatremia Fever Diabetes Insipidus Glycosuria Creatinine increased Hyperglycemia Hyperchloremia Hypokalemia	No History	BS = 102mg% (called slightly elevated)	none	10mg daily	90 days	amanta chlordi trazod levoth lorazep acetam lithiun propra magne alumir

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
37	US97044282A	49	M	Hyperglycemia	NIDDM	random BS = 500mg% x 2 times	none	15mg daily	90 days	valpro fluoxet insulin treatm acutely
38	US97045254	NR	NR	Hyperglycemia	Diabetes of unknown type	unknown	none	unknown	30 days	unkno
39	US97045842A	16	M	Hyperglycemia Hypoglycemia	No History	unknown	unknown	20mg daily	unknown	benztr valpro imipra dextro
40	US97050193A	56	M	Hyperglycemia	NIDDM	random BS= 198mg%	none	5mg BID	14 days	NPH i digoxi isosorb

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
41	US97050853A	16	M	Hyperglycemia Somnolence Creatinine increased	No History	random BS = 500mg%	none	unknown	6 months	imipra valpro dextro
42	US97052137A	32	M	Hyperglycemia	No History	unknown (Treatment consideration of acarbose suggests mild elevation)	none	7.5 mg daily	4 months	none
43	US97052272A	60	M	Hypoglycemia Coma	No History	18mg%	none	10mg BID	unknown	benztr isosorb lithiun chloral ciprofl halope diltiaz docusa terazos valpro

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
44	US97052743A	50	M	Hyperglycemia SGOT increased SGPT increased	NIDDM	500mg%	none	20mg daily	15 days	clozap
45	US97055761A	74	F	Hypoglycemia Confusion Somnolence	NIDDM	40mg%	none	5mg daily	3 days	furose potassi glybur metfor digoxi aspirin simvas magne benztr fluphe ferrous captop

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
46	US97060070A	22	M	Hyperglycemia Diabetes Mellitus Diabetic Acidosis Thirst Urinary frequency Paresthesia Nausea Vomiting	No History	1050mg%	none	10mg daily	18 days	clozap valpro
47	US97060994A	NR	F	Hyperglycemia Hypoglycemia	IDDM	unknown	none	10mg daily	4 months	cisapri insulin
48	US97062497A	16	F	Hyperglycemia Diabetes Mellitus Diabetic Acidosis	No History except (family history)	700mg%	none	10mg daily	10 weeks	carban sertrali
49	US97062563A	45	F	Hyperglycemia	No History	500mg%	none	15mg daily	unknown	clonaz halope benztr clozap
50	US97064489A	18	F	Hyperglycemia	unknown	unknown	none	unknown	unknown	unkno

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
51	US97065620A	40	M	Hyperglycemia Diabetic Acidosis Diabetes Mellitus	No History (no family history)	600mg%	none	20mg daily	3 months	none
52	US97071846A	28	M	Hyperglycemia Somnolence	IDDM (7yrs)	am BS = 300mg%	none	10mg daily	3 months	insulin
53	US97074024A	16	M	Hyperglycemia Hypoglycemia Epistaxis	No History (no family history)	Random BS = 300mg% and low BS = 21mg%	none	10mg daily	7 days	sertrali

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
54	US97074243A	58	F	Dehydration Somnolence Joint disorder NMS Fever Respiratory Acidosis Creatinine Phosphokinase increased Hyperglycemia Acidosis Leukocytosis Malaise Incoordination Vomiting Hyperventilation Lactic dehydrogenase increased Hyperuricemia Hypercalcemia BUN increased Creatinine increased Erythrocytes abnormal Glycosuria Hyperphosphatemia	No History of diagnosed diabetes. BS noted to be high in past (no family history)	1600mg%	none	unknown	25 days	captop indapa

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1C}$ VALUE	Dose	Duration	Conco Medic
55	US97084135A	35	M	Hyperglycemia Polyuria Thirst Ketosis Intentional overdose (25mg daily)	NIDDM (strong family history)	1400mg%	none	25mg daily	60 days	valpro clonaz
56	US97084138A	65	F	Hyperglycemia	NIDDM	300mg%	none	5mg daily	14 days	unkno antihy oral hy
57	ZA97062884A	67	M	Hyperglycemia	NIDDM	unknown	none	5mg BID	1 day	sertrali NPH i regula zopicl

1.1.3. Hyperglycemia[1] Case Summary

Patient Category	# Of Reports/Patient Cases	% Of Total Reports/Cases	Report/Case #
Known diabetic patient (IDDM or NIDDM)	28	52%	1, 4, 5, 7, 8, 18, 19 ($HgbA_{1C}$=12.3), 20, 21, 24, 25, 26, 27, 29, 31, 32, 33, 34, 37, 38, 40, 44, 47, 50, 52, 55, 56, 57
Risk factors for diabetes mellitus (DM)*	13	24%	2, 12, 17, 23, 39, 41, 42, 46, 48, 49, 51, 53, 54
Confounding factors that may increase BS or rule out any association with olanzapine**	8	15%	6, 10, 14, 22, 28, 30, 35, 36
No history of DM and no risk factors for DM	3	5%	11, 13, 15
Insufficient information to categorize	2	4%	3, 16
Totals	54 CASES	100%	

**Risk factors* = Obesity and/or family history

***Confounding factors* = Pancreatitis, dietary binges, sepsis, endocrine problems etc. or events took place prior to start of olanzapine.

1 Includes all 54 reports/cases containing one or more of the events hyperglycemia, diabetic coma, diabetic acidosis, and diabetes mellitus; excludes the 3 reports/cases where the only event was hypoglycemia.

There are three reports/patient cases with no history of diabetes and without any apparent risk factors for hyperglycemia. The reports/cases (11, 13, and 15) include a 75 year old male, a 78 year old male and a 65 year old female.

1.2. Weight Gain

Weight gain as a COSTART Event Term was also considered to determine whether there was a correlation between weight gain and hyperglycemia in the olanzapine reports/patient cases. Weight gain appeared 237 times as a COSTART Event Term through August 31, 1997 in the spontaneous reports/cases in DEN.

Weight gain was found in two of the 54 hyperglycemia reports/patient cases. Therefore, in only two of the 237 times weight gain was used as an event term was it also an event in a blood sugar alteration reports/cases. This incidence in the DEN database reports does not support a correlation of weight gain with hyperglycemia.

2. Summary

There are 54 reports/patient cases suggesting hyperglycemia in the spontaneous DEN database through August 31, 1997. In 49 of these reports/cases, patients were diabetic and/or had other apparent reasons for blood sugar elevations. In 2 of the 54 reports/cases, minimal information was provided, precluding any actual assessment of etiology or risk factors. In the remaining 3 report/cases, hyperglycemia cannot be readily explained. Given the extensive worldwide exposure to olanzapine through August 31, 1997 (634,000 patients); the number of reports/cases of hyperglycemia in the database is extremely small even when one considers all 54 reports/cases. Post-marketing spontaneous adverse event reports of alterations of blood glucose are consistent with the safety profile observed in clinical trials.