DRAFT

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

October, 1997

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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	Concomitant Medication	Comments
1	CA97064522 A	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	clonazepam, venlafaxine, olanzapine	patient started on glyburide 2.5mg after high BS
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.	fluoxetine oral hypoglycemic (name unknown)	Consumer report. weight gain noted: (115 lbs to 198 lbs over 6 months)
3	DE97082419 A	51	M	Hyperglycemia	No History	Prior to breakfast = 300mg%; after breakfast = 90mg% and after lunch = 50mg%	none	unknown	unknown	unknown	blood sugars suggest hypoglycemia as well as hyperglycemia

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
4	ES97071102A	34	F	Hyperglycemia	IDDM	600 without units	none	20mg daily	10 weeks	insulin	Patient was anxious; BS found to be elevated. Olanzapine was discontinued for 15 days and BS normalized. Rechallenge showed BS elevation
5	ES97072179A	34	F	Hyperglycemia	IDDM	400mg%	none	unknown	3 days	regular insulin diazepam sulpiride pyridoxine	Olanzapine discontinued with BS returning to normal
6	GB97012851 A	NR	M	Hyperglycemia Hypertension	No History	198mg%	none	10mg daily	2 days: events started prior to olanzapine treatment	lorazepam droperidol atenolol amlodipine	Physician noted that events and olanzapine start rules out the drug
7	GB97062119 A	62	M	Hyperglycemia	NIDDM	180mg%	none	10mg daily	6 months	glibenclamide	BS change noted by patient with home monitoring
8	US96114288 A	45	M	Hyperglycemia	NIDDM	unknown	none	10mg daily	unknown	fluvastatin diphenhydramine valproate sodium glyburide	Hospitalized with elevated BS and discharged
9	US96121894 A	NR	F	Hypoglycemia Hypotension Coma	unknown	unknown	none	5mg daily	1 day	clozapine phenytoin lithium, ranitidine	Patient became unresponsive except to pain stimuli. Outcome unknown.

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
10	US96123052 A	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 dietary supplement	Ensure consumption has been high since start of olanzapine. Ensure: 143 grams CHO per liter with source of CHO being sucrose and corn syrup
11	US96123673 A	75	M	Hyperglycemia Diabetes Mellitus	No History	560mg%	none	5mg daily	23 days	risperidone paroxetine	Spouse noted patient had been consuming large quanities of water for some time.
12	US96123925 A	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	carbamazepine ranitidine. furosemide clonazepam venlafaxine potassium nadolol	Obese patient (5'0" - 278lbs). Carbamazepine initiated at the same time as olanzapine.
13	US96124591 A	78	M	Hyperglycemia	No History	Peak random BS = 560mg% with baseline value of 200mg%	none	5mg daily	14 days	unknown insulin started to treat hyperglycemia	Patient was hospitalized and olanzapine was stopped.

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
14	US97011171	34	M	Hyperglycemia Diarrhea Dehydration Malaise Convulsion	No History	Random BS: 1400mg%	none	7.5mg daily	6 weeks	lithium	Patient began "Kool-Aid" drinking binge 2 wks prior to 1400mg% BS. Patient hospitalized and placed on insulin. Sugars normalized and patient discharged without insulin treatment.
15	US97012470 A	65	F	Hyperglycemia	No History	Random BS = 400mg%	none	10mg daily	60 days	thiothixene aspirin furosemide digoxin trihexyphenidyl	Patient experienced difficulty controlling BS while on olanzapine. Olanzapine discontinuation improved BS
16	US97014858 A	NR	NR	Hyperglycemia	No History	FBS= >200mg%	none	unknown	unknown	none	Olanzapine was stopped. BS outcome unknown
17	US97014882 A	33	M	Hyperglycemia Nausea Hypercholesteremia	No History	Random BS = 500mg%	none	10mg daily	5 weeks	zolpidem potassium clonazepam indapamide fluvastatin felodipine mirtazapine	Patient is obese (6' - 250lbs) with significant history of hyperlipidemia

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
18	US97015026 A	NR	NR	Hyperglycemia	IDDM	unknown	none	unknown	unknown	insulin	Drug stopped. Outcome unknown
19	US97021057 A	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	carbamazepine lithium levothyroxine atenolol trazodone alprazolam, haloperidol History spironolactone althiazide	Managed with IV insulin and discharged on insulin treatment. Original differential diagnosis included hyperosmolar coma, NMS, and sepsis.
20	US97021303 A	48	M	Hyperglycemia Somnolence Emotional Lability	NIDDM	225mg%	none	5mg daily	10 days	glyburide acetaminophen	Usual postprandial BS in this patient is 180mg%.
21	US97022137 A	17	M	Hyperglycemia	IDDM	Random BS= 300mg%	none	5mg BID	14 days	nefazodone insulin valproate sodium fluvoxamine benztropine	Report is lacking sufficient BS readings to establish any change
22	US97022578 A	45	M	Hyperglycemia Ketosis Coma Fever	No History	Upon admit to hospital: 900mg%	none	20mg daily	unknown	chlorpromazine lorazepam lithium	Physician suspected NMS. Patient died in hospital. Patient had ketoacidosis

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
23	US97022638 A	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	amlodipine furosemide (risperidone and lithium recently stopped)	Quick weight gain of 20 lbs just prior to elevated BS. Patient was in obese category prior to weight gain
24	US97022944 A	NR	M	Hyperglycemia	IDDM	unknown	none	unknown	unknown	insulin	Insulin dose adjusted to control BS.
25	US97024867 A	49	M	Hyperglycemia	NIDDM	random BS > 300mg%	none	unknown	3 weeks	glyburide allopurinol clonazepam thioridazine spironolactone labetalol potassium cl bumetanide fluoxetine	Glyburide and diet had controlled BS until addition of olanzapine. Primary MD will convert patient from glyburide to insulin treatment
26	US97030154 A	72	F	Hyperglycemia	NIDDM (6 yrs duration)	random BS = 524mg%	none	7.5mg daily	20 days	haloperidol	Highest BS took place after olanzapine dose increased from 5mg to 7.5 mg daily

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
27	US97031054 A	65	F	Hyperglycemia Anemia Hypokalemia Intentional Overdose (30mg daily)	NIDDM	unknown	none	10mg TID (30mg/day)	25 days	perphenazine regular insulin NPH insulin	Patient required a change from oral hypoglycemic to insulin. BS control changed while on 20mg daily.
28	US97031177 A	NR	NR	Hyperglycemia Elevated Pancreatic Enzymes	unknown	unknown	unknown	unknown	unknown	unknown	Patient hospitalized: Outcome unknown.
29	US97031237 A	54	M	Hyperglycemia Drug Interaction	NIDDM	random BS = 230mg%	none	7.5mg daily	60 days	glipizide trihexyphenidyl	BS control was lost and glipizide dosing was increased following addition of olanzapine
30	US97031381 A	42	F	Hyperglycemia Pancreatitis Fever Sepsis Amylase increased Somnolence Stupor	No History	random BS = 1672mg%	none	20mg daily	14 days	thiothixene clonazepam valproate sodium	Patient admitted to hospital with hyperosmolar coma and probable pancreatitis. Insulin IV drip controlled BS.

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
31	US97033103 A	37	F	Hyperglycemia	NIDDM	random BS = 304mg%	none	10mg daily	30 days	clozapine clonazepam benztropine insulin	Obese patient noted to not be following proper diet and on olanzapine.
32	US97033517 A	50	F	Hyperglycemia	NIDDM	random BS = 359mg%	none	unknown	60 days	insulin: sliding scale to control BS	Stable patient prior to olanzapine. Stopping olanzapine for 7 days inproved BS and rechallenge again created an elevation of BS.
33	US97034576 A	NR	M	Hyperglycemia	NIDDM	unknown other than "spiked" a BS	none	unknown	unknown	clonazepam nifedipine	Patient was well controlled on diet. "Spiked" BS not well defined.
34	US97035644 A	79	F	Hyperglycemia	NIDDM	random BS = >300mg% at multiple times	7.6	unknown	30 days	lente insulin pravastatin risperidone phenelzine thyroid	Well controlled diabetic patient lost control of BS. Olanzapine discontinued and BS control resumed.

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
35	US97041084 A	21	F	Hyperglycemia	No History	FBS= 270mg% and bedtime (HS) sugar = 400mg%	none	20mg daily	8 weeks	valproate sodium trihexyphenidyl paroxetine flurazepam thyroid	Autistic patient with enlarged thyroid gland lost control of BS on olanzapine. Olanzapine discontinued. Outcome unknown.
36	US97043244 A	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	No History	BS = 102mg% (called slightly elevated)	none	10mg daily	90 days	amantadine chlordiazepoxide trazodone levothyroxine lorazepam, acetaminophen lithium propranolol magnesium/ aluminum hydroxides	Patient diagnosed with nephrogenic diabetes insipidus.

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
				Hypokalemia							

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
37	US97044282 A	49	M	Hyperglycemia	NIDDM	random BS = 500mg% x 2 times	none	15mg daily	90 days	valproate sodium fluoxetine insulin (added after to treatment high BS acutely)	Patient improved and is now on glyburide.
38	US97045254	NR	NR	Hyperglycemia	Diabetes of unknown type	unknown	none	unknown	30 days	unknown	Outcome unknown.
39	US97045842 A	16	M	Hyperglycemia Hypoglycemia	No History	unknown	unknown	20mg daily	unknown	benztropine valproate sodium imipramine dextroamphetamin e	204 kg black female required insulin. Timing of BS change in relation to olanzapine start is unknown. Patient BS now controlled by diet.
40	US97050193 A	56	M	Hyperglycemia	NIDDM	random BS= 198mg%	none	5mg BID	14 days	NPH insulin, digoxin isosorbide dinitrate	Blood sugars prior to olanzapine were stable at 150mg%. Timing of sugars unknown

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
41	US97050853 A	16	M	Hyperglycemia Somnolence Creatinine increased	No History	random BS = 500mg%	none	unknown	6 months	imipramine valproate sodium dextroamphetamin e	Obese patient (5'7" - 240lbs) hospitalized due to extreme drowsiness and elevated BS. Olanzapine and imipramine stopped.
42	US97052137 A	32	M	Hyperglycemia	No History	unknown (Treatment consideration of acarbose suggests mild elevation)	none	7.5 mg daily	4 months	none	Consumer report. Patient is obese (5'8" - 200lbs) and states physician is considering starting patient on acarbose for elevated sugars.
43	US97052272 A	60	M	Hypoglycemia Coma	No History	18mg%	none	10mg BID	unknown	benztropine isosorbide lithium chloral hydrate ciprofloxacin haloperidol, diltiazem docusate sodium terazosin valproic acid	Patient hospitalized for psychiatric reasons and hypoglycemia developed while in hospital. Roommate on an oral hypoglycemic and medication misadventure has been suggested.

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
44	US97052743 A	50	M	Hyperglycemia SGOT increased SGPT increased	NIDDM	500mg%	none	20mg daily	15 days	clozapine	BS elevated between 240mg% and 500mg% during time of transition between clozazpine and olanzapine Treatment. Patient being weaned from clozapine. BS normalized after clozapine completely stopped.
45	US97055761 A	74	F	Hypoglycemia Confusion Somnolence	NIDDM	40mg%	none	5mg daily	3 days	furosemide potassium glyburide metformin digoxin aspirin simvastatin magnesium gluconate benztropine fluphenazine ferrous sulfate captopril	Patient has recently reduced caloric intake and had a weight loss. Events thought to be associated with caloric changes.

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
46	US97060070 A	22	M	Hyperglycemia Diabetes Mellitus Diabetic Acidosis Thirst Urinary frequency Paresthesia Nausea Vomiting	No History	1050mg%	none	10mg daily	18 days	clozapine valproate sodium	Obesity (5'10" - 200lbs). Placed on insulin drip. Patient stabilized on NPH insulin 64 units daily.
47	US97060994 A	NR	F	Hyperglycemia Hypoglycemia	IDDM	unknown	none	10mg daily	4 months	cisapride insulin	Level of BS changes not specified.
48	US97062497 A	16	F	Hyperglycemia Diabetes Mellitus Diabetic Acidosis	No History except (family history)	700mg%	none	10mg daily	10 weeks	carbamazepine sertraline	Obese patient (5'6" - 218lbs). Elevation of BS and presence of ketones seen.
49	US97062563 A	45	F	Hyperglycemia	No History	500mg%	none	15mg daily	unknown	clonazepam haloperidol benztropine clozapine	Outcome unknown. 5'9" - 180lbs
50	US97064489 A	18	F	Hyperglycemia	unknown	unknown	none	unknown	unknown	unknown	History of drug abuse. BS change managed by diet only. Tests performed indicating presence of hyperglycemia prior to olanzapine

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
											(HgbA1C ?)

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
51	US97065620 A	40	M	Hyperglycemia Diabetic Acidosis Diabetes Mellitus	No History (no family history)	600mg%	none	20mg daily	3 months	none	Obese patient. Patient BS had been checked on a quarterly basis and had been WNL. Normal 4 wks prior to 600mg%. Diagnosed with DM and placed on insulin.
52	US97071846 A	28	M	Hyperglycemia Somnolence	IDDM (7yrs)	am BS = 300mg%	none	10mg daily	3 months	insulins	BS has not been below 170mg% for last 3 months.
53	US97074024 A	16	M	Hyperglycemia Hypoglycemia Epistaxis	No History (no family history)	Random BS = 300mg% and low BS = 21mg%	none	10mg daily	7 days	sertraline	Obese (5'8"-210lbs).Olanzapine withdrawn following 300mg% and BS went to 21mg%. Epistaxis took place when BS was elevated.

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
54	US97074243 A	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	captopril indapamide	Obese patient (5'6" - 250lbs). Hospitalized with NMS vs heat stroke. Many labs abnormal.

#	Mfr. Report #	Age	Sex	COSTART Event Terms	Diabetic History	Peak blood sugar (BS) or lowest BS	$HgbA_{1c}$ VALUE	Dose	Duration	Concomitant Medication	Comments
55	US97084135 A	35	M	Hyperglycemia Polyuria Thirst Ketosis Intentional overdose (25mg daily)	NIDDM (strong family history)	1400mg%	none	25mg daily	60 days	valproate sodium clonazepam	Prior to these events; patient was not on therapy for DM. Insulin therapy started in hospital
56	US97084138 A	65	F	Hyperglycemia	NIDDM	300mg%	none	5mg daily	14 days	unknown antihypertensive and oral hypoglycemic	Patient noted to have many endocrine problems.
57	ZA97062884A	67	M	Hyperglycemia	NIDDM	unknown	none	5mg BID	1 day	sertraline NPH insulin regular insulin zopiclone	Insulin dosing required adjusting. Patient not under good control upon olanzapine initiation.

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.

CS
VS

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

TELEFAX MESSAGE

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RE:	OLANSEK/ZYPREXA - Second Periodic Safety Update Report covering the period from 27 March 1997 to 26 September 1997		
CC:	Dr Markku Toivonen Ms Priya Bahri, EMEA Pharmacovigilance Sector		

Number of Pages (including cover sheet): 2

Message:

Dear Ms Shaw-Stewart,

We refer to the documentation submitted for Olansek and Zyprexa concerning:

- the second periodic safety update reports covering the period from 27 March 1997 to 26 September 1997;

We inform you that the CPMP, during its meeting from 26 – 28 January 1998, concluded that the areas of concern after the first PSUR (ventricular arrhythmias, haematological toxicity, liver toxicity and interactions) give no new signals or concern in present PSUR. The risk/benefit balance remains unchanged. New areas of concern have been properly evaluated by Lilly. The reported cases of liver toxicity, however, should be reflected more clearly in the SPC through a type II variation. An addition to Section 4.8 is suggested: "Rare reports of hepatitis have been received" and references in Section 4.8 to other neuroleptics should be deleted.

Hyperglycaemia, seizures/convulsions, liver toxicity and haematologic variations (including thrombocytopenia) should be monitored carefully and reported in the next PSUR.

If you have any queries regarding the above, please do not hesitate to contact us, or the Rapporteur Dr Markku Toivonen.

Yours sincerely,

Tony Humphreys

IF THIS FAX IS ILLEGIBLE OR INCOMPLETE, PLEASE CALL THE PHONE NUMBER ABOVE

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