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## **Olanzapine Labeling Change on Dementia for 14-JAN-2004 GPLC**

### **Chronology of Regulatory Correspondence Regarding Olanzapine and Cerebrovascular Adverse Events**

## June 2002: Health Canada

### **Document Title: Evaluation of Olanzapine and Cerebrovascular Adverse Events, Hypotension, and Hyperglycemia and/or Weight Gain**

This report was prepared in response to an e-mail request received on 26 April 2002 from Health Canada, and provided information requested by its Bureau of Pharmaceutical Assessment.

Within the olanzapine clinical trial database, incidence of CVAE (olanzapine versus placebo, olanzapine versus haloperidol, olanzapine versus clozapine, or olanzapine versus risperidone) was calculated within schizophrenia, bipolar, and elderly groups. Comparative incidence analyses were also conducted across age groups. This report also included analyses of Clintrace postmarketing data on CVAEs in olanzapine-treated patients.

In the clinical trials database, treatment-emergent CVAEs on olanzapine were observed infrequently (incidence <1%). A total of 14 patients with CVAEs were identified in the clinical trials database: 9 olanzapine-treated patients, 4 risperidone-treated patients, and 1 patient receiving placebo. All 9 olanzapine-treated patients with CVAE had one or more preexisting risk factors for cerebral ischemic events.

In haloperidol-controlled schizophrenia trials, olanzapine-treated patients had increasing incidence of CVAE associated with increasing age range. Due to the small sample size (<5), the test for statistically significant linear trends may not have been robust. Within the bipolar diagnostic group, there was no reported incidence of CVAE in any treatment group (olanzapine, haloperidol, or placebo). In the elderly group, CVAEs were reported in the olanzapine (n=4), risperidone (n=4), and the placebo treatment groups (n=1).

Review of Clintrace postmarketing adverse event data showed a very rare (<.01%) reporting rate for cerebrovascular adverse events.

Two olanzapine-treated patients and 1 risperidone-treated patient were identified with both CVAE and hypotension. Of the 2 patients on olanzapine, one patient had a concomitant medical condition (rectal hemorrhage), which was likely a causative factor in the orthostatic hypotension. The second patient had documented orthostatic hypotension during hospitalization for the CVAE; the hypotensive episode was possibly related to the concomitant use of nitrates. These results were consistent with the known potential for orthostatic hypotension in a proportion of individuals treated with olanzapine, which was reflected in the current labeling for olanzapine.

Treatment-emergent CVAEs on olanzapine were observed infrequently (incidence <1%) in the clinical trial database, and very rarely (reporting rates <.01%) in the postmarketing spontaneous adverse event database. This review provided no basis to implicate olanzapine as a cause of cerebrovascular adverse events in the presence or absence of hypotension.

## December 2002: US FDA

### **Document Title: Evaluation of Olanzapine and Cerebrovascular Adverse Events in Patients with Dementia**

This report was prepared in response to a 3 July 2002 letter from the FDA Division of Neuropharmacological Drug Products. The Division requested that Lilly examine its clinical trials database for evidence of an association between treatment with atypical antipsychotics and cerebrovascular adverse events (CVAEs) in patients with dementia.

Olanzapine-placebo comparisons presented in this report showed numerically greater crude and annualized incidence of CVAEs in olanzapine-treated patients compared with placebo-treated patients (for individual events of CVA, haemorrhagic stroke, ischaemic stroke, transient ischemic attack; and for total events). Table 1 shows that none of these treatment-group differences were statistically significant (total events: olanzapine 1.3% versus placebo 0.4%;  $p=0.177$ ).

All cases of CVAE identified in the olanzapine treatment groups had one or more prerandomization risk factors for cerebral ischaemic events (as did placebo-, risperidone-, and conventional antipsychotic-treated patients). In addition, all of these cases presented with definite or possible other etiologic contributing factors, including concomitant medications or concurrent medical conditions known to be temporally associated with the risk of CVAE.

In the olanzapine-placebo comparison group, logistic regression analysis showed that a patient's age was significantly associated with likelihood for CVAE: patients  $\geq 80$  years of age had a nearly 4-fold greater likelihood for CVAE than did individuals  $< 80$  years.

The presence of vascular or mixed dementia was significantly associated with a greater likelihood of CVAE: patients with diagnoses of vascular or mixed dementia had a more than 5-fold greater likelihood of experiencing a CVAE than did patients with a diagnosis of Alzheimer's. This observation is the most consistent finding in these regression analyses, with similar odds ratios (ORs) observed in the olanzapine-risperidone comparison and in the Olanzapine Overall Integrated Database, and is not surprising given the underlying pathophysiology of vascular/mixed dementia. Thus, a non-Alzheimer's diagnosis (ie, vascular or mixed dementia) appeared to be a strong predictor of likelihood of CVAE. The presence of orthostatic hypotension was not a significant predictor of likelihood of CVAE. No other explanatory variables were significantly associated with the likelihood of CVAE. This report concluded that the available data did not demonstrate a causal relationship between treatment with olanzapine and cerebrovascular adverse events. Data presented in this review were consistent with olanzapine's known safety profile and current labeling in the US.

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**Table 1. Incidence of Treatment-Emergent Cerebrovascular Adverse Events  
Double-Blind Treatment Periods  
Olanzapine versus Placebo  
Olanzapine Double-Blind Comparator Database**

FDA CEREBROVASCULAR ANALYSES  
Incidence of Treatment-Emergent Adverse Events  
Double-Blind  
Olz/Placebo studies

per Event Pat Yr	P-Value** Classification (IR)	Therapy	Duration of Exposure (Yr/Pat)	Incidence			P-Value* (CI)	Incidence 1000
				N	n	(%)		
27.0	.340	1) Olz	0.28	1178	9	0.8	.298	
7.4		2) Placebo	0.28	478	1	0.2		
3.0	1.00	1) Olz	0.28	1178	1	0.1	1.00	
0.0		2) Placebo	0.28	478	0	0.0		
3.0	1.00	1) Olz	0.28	1178	1	0.1	1.00	
0.0		2) Placebo	0.28	478	0	0.0		
12.0	1.00	1) Olz	0.28	1178	4	0.3	1.00	
7.4		2) Placebo	0.28	478	1	0.2		
45.0	.188	1) Olz	0.28	1178	15	1.3	.177	
14.9		2) Placebo	0.28	478	2	0.4		

N - Total number of patients.  
n - Number of events.  
% - (crude) incidence.  
\* - P-values testing crude incidence between therapy groups using Fisher's exact test.  
\*\*- P-values testing incidence rate between therapy groups using normal approximation or exact binomial calculation.

Studies included:

HGAO HGEU HGGU HGIC HGIV.

Events include the following MedDRA terms:

'AORTIC THROMBOSIS' 'ARTERIAL ANEURYSM NOS' 'ARTERIAL OCCLUSION NOS' 'ARTERIAL THROMBOSIS NOS'  
'BRAIN STEM INFARCTION' 'CAROTID ARTERY OCCLUSION' 'CEREBRAL ARTERIAL ANEURYSM' 'CEREBRAL  
HAEMORRHAGE'  
'CEREBRAL INFARCTION' 'CEREBRAL ISCHAEMIA' 'CEREBROVASCULAR ACCIDENT' 'HAEMORRHAGIC STROKE'  
'INTRACRANIAL HAEMORRHAGE NOS' 'ISCHAEMIC STROKE NOS' 'TRANSIENT ISCHAEMIC ATTACK'.

RMP.F1DSCRT2.SASPGM(ISSE03EL) 15848

## June 2003: US FDA

### **Document Title: Symbyax Response: Package Insert Language – Cerebrovascular Events in Elderly Patients with Dementia**

This document was prepared in response to FDA's proposed Symbyax labeling language regarding CVAEs in elderly patients with dementia.

As reported in the December 2002 document to the FDA, all CVAE cases in olanzapine-treated patients were confounded by concurrent medical conditions and/or concomitant medications having a temporal association with CVAE, and/or presented with risk factors for CVAE. In particular, of the 22 olanzapine-treated patients experiencing a CVAE, 18 patients had a history of hypertension at baseline; 6 of these 18 patients with a history of hypertension also had a previous history of CVAE. One additional patient had a previous history of CVAE. The remaining 3 olanzapine-treated patients had other baseline conditions known to be associated with an increased risk of CVAE (eg, smoking, obesity, congestive heart failure with cardiomegaly, atherosclerotic heart disease, and peripheral vascular disease). Because of the historical and concurrent medical conditions in these patients, a potential contribution of olanzapine therapy to the development of CVAE cannot be established.

Based on this information, Lilly proposed the inclusion of the following statement within FDA's proposed label for Symbyax:

All patients who experienced a cerebrovascular event had preexisting risk factors known to be associated with an increased risk for CVAE (eg, history of previous CVAE or transient ischemic attack, hypertension, cigarette smoking) and presented with concurrent medical conditions and/or concomitant medications having a temporal association with CVAE.

Lilly proposed that information on CVAEs would be most appropriately placed in the "Precautions" section of the Symbyax Package Insert, based on the following interpretation of 21 CFR 201.57:

- Warnings are warranted by "reasonable evidence of an association of a serious hazard with a drug." As previously described, the incidence of CVAE in olanzapine-treated patients was not statistically significantly different than the incidence observed in placebo-treated patients. Based on detailed clinical evaluation of the 22 olanzapine cases of CVAE in this dataset, it was determined that all 22 cases were highly confounded by the presence of preexisting risk factors or concomitant medications/medical conditions known to be associated with an increased risk of CVAE. Therefore, it is not possible to establish "reasonable evidence" that treatment with olanzapine is a possible contributing factor to CVAE.

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- "Precautions," on the other hand, would include "information regarding any special care to be exercised by the practitioner for safe and effective use of the drug." Clinical evaluation of these cases makes clear that all patients who experienced a CVAE had preexisting risk factors, concomitant medical conditions, and/or concomitant medications that would predispose them to risk of CVAE. Clinicians provided with this knowledge may appropriately select or exclude patients for treatment based on the individual patients' risk factors. Under this interpretation of 21 CFR 201.57, inclusion of information on cerebrovascular adverse events in elderly patients with dementia would be more appropriately placed in the "Precautions" section of the Symbyax Package Insert.

## November 2003: US FDA

### **Document Title: Response to Request for Additional Information on Cerebrovascular Adverse Events in Patients with Dementia**

This document was prepared in response to a request from FDA for additional information regarding Lilly's submission to the FDA, "Evaluation of Olanzapine and Cerebrovascular Adverse Events in Patients with Dementia" (received by FDA on 17 December 2002).

Questions #1, #2, and #4 requested by-study incidence rates of CVAE, rates of serious and nonserious cases by study, and a clarification of the definition of the variable "presence of orthostatic hypotension," respectively. No additional significant findings were observed when examining CVAE incidence rates (either serious or nonserious) by study.

Question #3 requested that Lilly "Provide CVAE rates and 95% confidence intervals using Poisson regression, while adjusting for age and type of dementia. Simultaneous adjustment for the other covariates should be attempted in the model and those covariates should be kept in the model if found to be statistically significant." Information provided in response to this request follows:

The Genmod procedure in SAS Version 8 was used to estimate the CVAE rate and 95% confidence intervals. Thus, 80-year-old patients with Alzheimer's dementia who are using olanzapine would have an estimated CVAE rate of 41.22 per 1000 patient-years (95% confidence interval: 23.38 to 72.66 per 1000 patient-years) compared with a similar patient population using placebo, which would have an estimated CVAE rate of 10.78 per 1000 patient-years (95% confidence interval: 2.60 to 44.75 per 1000 patient-years).

Table 2 shows parameter estimates of the log CVAE rates, controlling for age and type of dementia. Olanzapine increases the log CVAE rate by 1.3407 compared with placebo, corresponding to a CVAE rate ratio of 3.82 ( $= e^{1.3407}$ ) for olanzapine compared with placebo.

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**Table 2. Parameter Estimates Using Poisson Regression Controlling for Age and Type of Dementia**

<b>Parameter</b>	<b>DF</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>Wald 95% Lower Confidence Limit</b>	<b>Wald 95% Upper Confidence Limit</b>	<b>Chi-square value</b>	<b>p-Value</b>
Intercept	1	-15.5780	2.8581	-21.1796	-9.9763	29.71	<.00
Olanzapine	1	1.3407	0.7500	-0.1292	2.8107	3.20	0.07
Placebo	0	0.0000	0.0000	0.0000	0.0000	.	.
Age	1	0.0994	0.0322	0.0364	0.1625	9.56	0.00
Alzheimer's Dementia	1	-2.8076	0.7519	-4.2813	-1.3338	13.94	0.00
Mixed Dementia	1	-2.1637	1.2274	-4.5693	0.2419	3.11	0.08
Vascular Dementia	0	0.0000	0.0000	0.0000	0.0000	.	.

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Of the remaining covariates previously tested using logistic regression (baseline MMSE, gender, and orthostatic hypotension), only gender was significant when added to a model that adjusted for age and type of dementia. Table 3 shows parameter estimates of the log CVAE rate when controlling for age, type of dementia, and gender. Olanzapine increases the log CVAE rate by 1.5733 compared with placebo, corresponding to a CVAE rate ratio of 4.82 ( $= e^{1.5733}$ ) for olanzapine compared with placebo.

For example, using the parameter estimates from the Poisson regression model that controls for age, type of dementia, and gender, the CVAE rate for 80-year-old males with Alzheimer's dementia using olanzapine would be 87.26 per 1000 patient-years (95% confidence interval: 44.05 to 172.89 per 1000 patient years) compared with a similar patient population using placebo, which would have a CVAE rate of 18.10 per 1000 patient-years (95% confidence interval: 4.09 to 80.14 per 1000 patient years).

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**Table 3. Parameter Estimates Using Poisson Regression Controlling for Age, Type of Dementia, and Gender**

<b>Parameter</b>	<b>DF</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>Wald 95% Lower Confidence Limit</b>	<b>Wald 95% Upper Confidence Limit</b>	<b>Chi-square value</b>	<b>p-Value</b>
Intercept	1	-16.6194	2.9105	-22.3239	-10.9149	32.61	<.0
Olanzapine	1	1.5733	0.7766	0.0512	3.0954	4.10	0.0
Placebo	0	0.0000	0.0000	0.0000	0.0000	.	.
Age	1	0.1208	0.0343	0.0535	0.1880	12.38	0.0
Alzheimer's Dementia	1	-2.9535	0.7767	-4.4757	-1.4312	14.46	0.0
Mixed Dementia	1	-2.1678	1.2435	-4.6049	0.2693	3.04	0.0
Vascular Dementia	0	0.0000	0.0000	0.0000	0.0000	.	.
Female	1	-1.3386	0.4818	-2.2829	-0.3943	7.72	0.0
Male	0	0.0000	0.0000	0.0000	0.0000	.	.

**To:** CN=Patrizia Cavazzoni/OU=AM/O=LLY@Lilly  
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**From:** CN=Christopher Carlson/OU=AM/O=LLY  
**Subject:** elderly abstract for NCDEU  
**Attachments:** A.Cavazzoni.elderly safety.NCDEU.040108.doc

Patrizia,

Here's the first draft of the abstract. Let me know if I am on the right track or if anything else needs to be added, deleted, or expanded. Should I talk to Carrie to get the p values highlighted in yellow? Thanks.

Chris



A.Cavazzoni.elderly safety.NCDEU.040108.doc

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