

FYE

Anna working on


Michele Sharp

11/29/99 04:25 PM

To: Gail M Uminger
Subject: Zyprexa

FYI--Notice short term action plan (c).


----- Forwarded by Michele Sharp/AM/LLY on 11/29/99 04:25 PM -----

 Gregory T Brophy
11/29/99 04:17 PM

To: H John Roth, Michele Sharp, J Alan Webber

Per the documents from Tim that I shared with you last week - here is the outcome of the meetings.
Thanks, Greg

----- Forwarded by Gregory T Brophy/AM/LLY on 11/29/99 04:16 PM -----

 Edmundo Muniz
11/28/99 09:56 PM

To: Michael D Clayman, Timothy R Franson cc: Gregory T Brophy, Kenneth Hornbuckle, Kenneth C Kwong, Edmund

Mike and Tim: bellow you will find a summary of issues discussed this week regarding Hyperglycemia and Zyprexa:

1. There are two types of initiatives:

a. **The Cross-functional Action Team lead by Alan Breier.** The goal of this team is to bring to the same table all the groups and functions working to address the hyperglycemia issue. This Action Team has a Steering Committee formed by N. Ascroft, A. Breier, J. Caro, R. DiMarchi, C. Fibiger, S. Paul, G. Probst, and G Tollefson. The following are the studies the team will be implementing in the near future:

1. Intervention: Pharmacological Interventions for Olanzapine-related Weight Gain (the goal of this study is to assess the efficacy of 2 doses of nizatidine compared to placebo in preventing olanzapine-associated weight gain as measured by change from baseline in total body weight)
2. Mechanistic: F1D-MC-HGIM: The goal of this study is to evaluate whether olanzapine and risperidone have adverse effects on insulin secretion and insulin sensitivity.
3. SNP discovery and genotyping: The goal of this study is to conduct genome sequencing and identification of Single Nucleotide Polymorphism (SNPs). These potential large-scale surveys of genomic variation may provide data enabling large-scale genetic association studies.

b. **The Regulatory/PhV and the Zyprexa Team:** While Val Simmons/Man Fung/Kenneth Kwong and Charles Beasley have been working closely together on this issue, it was felt that a broader involvement of regulatory/PhV (Mike Clayman, Tim Franson, Greg Brophy, and Edmundo Muniz) was needed to evaluate a short term plan.

2. Background

a. The discussion regarding hyperglycemia/weight gain and anti-psychotic drugs goes back as far as the early 1950's

For more than two decades, until the 1980's there was a large number of publications but the

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- interest of the scientific community and the regulators decreased until very recently.
- b. Two regulatory agencies (EMA and Canada) have proactively asked questions about hyperglycemia and Zyprexa
 - c. Charles Beasley reassured us that regulators have felt satisfied with Lilly's explanations and Lilly's commitment to conduct new clinical trials and to continue to do proactive post-marketing safety surveillance
 - d. Hyperglycemia and DKA are both in the US label
 - e. Hyper O. Coma is in the Bipolar IND submission (needs to be confirmed)

3. Short Term Action Plan

- a. Continue to strengthen the post-marketing safety surveillance of hyperglycemia, including targeted follow-up
- b. Explore the possibility of using GPRD to conduct data base analysis (natural history of hyperglycemia, sub-population analysis, frequency, severity, class effect, prevalence, incidence, competitors analysis, etc)
- c. Discuss Zyprexa Label at a GPLC session and evaluate potential proactive regulatory strategies
- d. Evaluate the regulatory utility of the new studies the Cross-functional Team is conducting

best regards,

Edmundo

*hyperglycemia added to
post mkt AE
precaution in Europe*

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	trans random gluc ≥ 200 mg/dl	Persistent or possibly pers. random gluc ≥ 200	Persistent or possibly persistent random glu ≥ 160 but < 200	Persistent or possibly persistent	trans random
n (4233) Olan.	0.93%	.98	1.3%	98%	1.09
n (478) Plac.	0.24%	0.00	1.0% 0.42	0.00	0.42%

intro Olan + H pts describe compared to placebo treat pts table elements 0% w/...

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