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

To: Gail M Uminger
Subject: Zyprexa

Michele Sharp

11/29/99 04:25 PM

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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

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Edmundo Muniz
11/29/99 09:56 PM

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

Mike and Tim: below 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 Tollefsen. 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
interest of the scientific community and the regulators decreased until very recently.
b. Two regulatory agencies (EMEA 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